UTMJ

University of Toronto Medical Journal

Volume 77, Supplement/January 11, 2000

A student-run scientific publication. Established in 1923.

Proceedings of the 14th Annual University of Toronto Medical Student Research Day

University of Toronto
MSRD
Medical Student Research Day

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The University of Toronto Medical Journal (UTMJ)

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All review and original articles received for publication in the 77th UTMJ Edition will be automatically considered for the Inaugural UTMJ Editors' Award. Submission deadlines for the 77th UTMJ Edition are:

Oct. 1st, 1999 Jan. 14th, 2000 April 3rd, 2000

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Program

11:00 a.m.-1:00 p.m.	**Registration and Poster Set-up** *Stone Lobby, Medical Sciences Building*
1:00 p.m.-2:00 p.m.	**Keynote Speaker: Dr. Doug Hamilton** "The History of Space Medicine and Its Challenge in the Future: What should Canada's Role Be?" *Room 3153, Medical Sciences Building*
2:00 p.m.-4:30 p.m.	**Poster Presentation** *Stone Lobby, Medical Sciences Building*
4:45 p.m.-5:30 p.m.	**Presentation by Winners of 1999 MSRD** *Room 2173, Medical Sciences Building* Theodoros Tsakiridis (0T1) Recipient of the 1999 Department of Medicine Sponsorship *"Alternative Pathways of MAP Kinase Activation by Tyrosine Kinase Receptors."* Richard Bitar (0T1) Recipient of the 1999 George Brown Memorial Award *"Androgen-induction of NF-κB is Important for Prostate Tumour Cell Survival."* Ally-Khan Somani (MD/PhD) Recipient of the 1999 George Brown Memorial Award *"The SHP-1 Tyrosine Phosphatase Inhibits Antigen Receptor-induced Apoptosis of Activated Peripheral Cells."*
5:30 p.m.-5:40 p.m.	**Raffle**
5:40 p.m	**Award Presentation and Wine & Cheese Reception** *Ruth Kurdyak Medical Alumni Lounge, Medical Sciences Building*

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University of Toronto

MSRD

Medical Student Research Day

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Keynote Speaker: Douglas Hamilton

B.Sc.Eng., M.Sc.Eng., P.Eng., M.D., Ph.D., F.A.C.P.
Flight Surgeon, NASA Johnson Space Center Medical Operations
Professor, International Space University

Dr. Douglas Hamilton is a Flight Surgeon at the NASA Johnson Space Center (JCS) Medical Operations supporting the Space Shuttle and the International Space Station (ISS). He attended the International Space University (ISU) in the Faculty of Life Sciences in 1992, and since 1996 has taught there in the area of Operational Space Medicine. Dr. Hamilton is presently working on designing and building the medical treatment facilities for the ISS and the future Mars mission. He has supported space shuttle missions, medical experiments, and also the manned Mars analog chamber tests at JSC. Dr. Hamilton is designing the medical support system for the 400-day manned Mars analog mission at the JSC. He is also participating in the design of the medical facilities of the next generation of emergency crew return vehicles for the ISS and the proposed Mars habitat. Dr. Hamilton is the lead technical consultant for the ISS electronic medical record and telemedicine system at NASA JSC.

In 1991, Dr. Hamilton graduated as an MD from the University of Calgary, Faculty of Medicine. During medical school, he concurrently completed a PhD in Cardiovascular Physiology at the University of Calgary. He is board certified in Internal Medicine in both Canada and the United States, but has spent most of his clinical time on acute care wards, emergency room, intensive care environments and rural clinics around Calgary.

In addition, Dr. Hamilton has been a practicing engineer for seventeen years and is professionally certified in Canada and the United States. He completed a B.Sc. in Electrical Engineering in 1980 at the University of Alberta, specializing in digital control systems and laser plasma physics. He received his M.Sc. in Electrical Engineering in 1983 at the University of Alberta, designing medical laser systems for surgery and photochemotherapy. Dr. Hamilton was the manager of Medical Academic Computer Services from 1983 until 1988 at the University of Calgary. He has also designed, built and used data acquisition systems for open-heart surgical suites to acquire physiological data on humans during open-heart surgery.

While training as a Mission Control Flight Surgeon for NASA, Dr. Hamilton received his Flight Surgeon wings with the US Air Force. He is one of twenty astronaut candidates for the Canadian Space Agency where he was selected from over five thousand applicants in 1992. Dr. Hamilton is trained in hyperbarics, high altitude physiology, and is certified to fly in high performance fighter aircraft. He has flown on the NASA KC-135 and Russian IL-76 aircraft simulating microgravity, using parabolic flight profiles to study the surgical aspects of microgravity, as well as the human factors of resuscitating a seriously ill patient in the ISS and during an interplanetary mission to Mars. He was also the lead clinical consultant for the team designing the telemedicine system for the Space Shuttle, and was one of the clinicians who evaluated the real-time data in mission control during the shuttle mission in January 1998. He presented the Medical Operations critical path for a Mars mission to the National Science and Biological Research Institute in 1998, which is now being used by NASA as a template for the planned 2015 mission to Mars. Dr. Hamilton is presently designing the telemedicine interface between the flight surgeon consoles of NASA and the Russian Space Agency. This flight surgeon console interface will eventually be expanded to include all the international partners for ISS. He is also currently investigating the feasibility of using portable collapsible hyperbaric chambers on-orbit to treat decompression sickness secondary to Extra-Vehicular Activity (EVA) and the use of diagnostic ultrasound on the ISS using the KC-135 to simulate trauma models in microgravity.

Dr. Hamilton has several patents pending in the area of remote power generator design and wireless power and corrosion monitoring systems. He also has developed solar powered pipeline valve actuation systems, which work in northern Canada, and corrosion protection systems, which can protect large pipelines. He has developed wireless medical devices such as glucose monitors, which can report results anywhere in the world using communication satellite technology. Dr. Hamilton has designed production line machinery for the Boeing Aircraft Corporation and presently consults to Motorola and MCI in the area of wireless communication and 2-way pager design for medical applications.

Dr. Hamilton grew up in Canada and enjoys playing ice hockey and has played for the Canadian national rugby team. He is presently living in Houston with his wife Kathy and three children (Keltie, Bridie and Ross). He has lectured about engineering and medicine in many parts of the world and has numerous publications and presentations in these fields. His main interest is the human aspects of space travel and the role it plays in improving the human condition on Earth.

Message from the Dean

David Naylor, M.D., D.Phil., FRCPC
Dean, Faculty of Medicine

Welcome to the 'Y2K' Medical Student Research Day! Each year the MSRD provides an opportunity for undergraduate medical students to display the results of their research. Student research activities showcased in the MSRD invariably mirror the Faculty itself in the breadth of topics covered - spanning population-based epidemiology, social and behavioural sciences, a huge variety of clinical studies, and fundamental biomolecular investigation.

It is perhaps not surprising that our students have embraced a wide range of research activities. Research, of course, is at the very heart of what we do in the Faculty of Medicine. The tally of researchers working in this Faculty includes hundreds of superb scholars and scientists based variously on the St. George Campus and an unparalleled array of institutions and agencies. The University-affiliated teaching hospitals have all embraced research as central to their missions. Together, the Faculty's researchers generate over $200,000,000 a year in external funding, a total exceeded worldwide by only a handful of other institutions.

Each year about 100 medical students receive scholarships through the Faculty of Medicine, enabling them to work on projects in a wide variety of settings. Others find ways to participate in research projects on their own terms, sometimes through electives and often by giving up their limited leisure time. Some MSRD participants entered Medicine with advanced degrees and have carried a thesis-based project to fruition since enrolment. Others again are enrolled in our MD/PhD program. However it is that the students presenting at MSRD got started on the path to research, they have all travelled a serious distance to generate the posters and abstracts presented on this day.

Andrew Baines, former Vice Dean of Education, put it well when he wrote in 1996: "The students participating in research day have taken time out from a demanding professional training programme to prepare and present their posters. The challenge for health care professionals engaged in research is to maintain a balance between clinical and investigative responsibilities. The students who participate in Research Day begin to experience this sometimes difficult, yet highly rewarding, duality."

For many participants, presenting at MSRD is a milestone, but their journey will continue. Drawing on the work displayed at MSRD, many students will go on to publish papers in peer-reviewed journals. We also know from past experience that a substantial number will decide to make research their life's work, entering one of the graduate or post-graduate research programmes offered in this Faculty.

In sum, the continuing success of MSRD reflects positively on our outstanding students, the research-intensivity of the Faculty of Medicine itself, and the commitment and support of so many faculty members who mentor and supervise student researchers. Congratulations to all the participants, and many thanks to the faculty members, staff and sponsors who make this year's event possible.

David Naylor, M.D., D.Phil., FRCPC
Dean, Faculty of Medicine

Message from the Associate Dean, Undergraduate Medical Education

Richard C Frecker, M.D., Ph.D.
Associate Dean, Undergraduate Medical Education

From time-to-time, I recognize something of which I am very proud; something that makes my "list." One, of course, is my family. However, it may come as a surprise to you (it shouldn't!) that *Medical Student Research Day* is on that short list! As a judge over the years, I've had the pleasure, and, yes, sometimes the challenge, of reviewing my share of the many high-quality research projects that are presented at MSRD. What continues to impress me is that these research efforts, and outcomes, are yet another aspect of what is already one of the busiest and most challenging educational programs.

So, it is with great satisfaction that I welcome you to MSRD-2000! This is your opportunity to feast on the excellent academic fare brought to you by a selection of more than 100 students, who engage each summer in research projects, many supported by the Faculty of Medicine's *Summer Scholarship Program.* They are joined by students from our MD/PhD program, who have committed themselves to attaining both degrees, in a combined program.

Each year, the authors of the two top-ranked projects are rewarded with an all-expenses-paid trip to Galveston, Texas. There, they present their work at the Annual Medical Student Research Forum (USA) – joined by a third award-winning student, who is sponsored by the Faculty's Department of Medicine. Our students not infrequently bring home top awards from this international forum!

The research that goes into this impressive display could not reach you without the organization, energy, and commitment of the Student Planning Group which plans and coordinates this event. Their activity began almost nine months ago, and it has been continuous. Thanks from us all!

Thanks, too, to the amazing cadre of judges who have given of their time to read, understand, and adjudicate the many submissions you will see on January 11th – and special thanks also to the keynote speaker, Dr. Douglas Hamilton, who will grace this occasion. The corporate donors who support this student endeavor are the fiscal glue that holds it together. Thanks to all and sundry for a great effort!

Richard C. Frecker, M.D., Ph.D.
Associate Dean, Undergraduate Medical Education

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Alternative Medicine

AM1

MULTIFACETED ALTERNATIVE THERAPY FOR POST-HERPETIC NEURALGIA: A PRELIMINARY STUDY. Fred Hui MD , Adam Cheng MD, Mark Chiu*, Eugene Vayda MD

Background: Post-herpetic neuralgia, persistent pain more than one month after the onset of herpes zoster (HZ), is debilitating, affects many elderly and is difficult to treat. **Objective**. To determine if the addition of alternative therapy to western medicine enhances the treatment of pain in postherpetic neuralgia (PHN). **Methodology**: A literature review was conducted on the Medline database from 1988-1998, searching for information on the current treatment of PHN The literature review found that although many medications have been used to reduce the pain of PHN, no treatments were satisfactory in decreasing pain and many have significant side effects. Data on pain reduction in PHN following treatment were compiled from a group of 56 PHN patients in the principal investigator's (FH) family medicine practice This case series describes the combination of several established techniques: acupuncture, local anaesthetic nerve block, cupping and bleeding, and Chinese herbs. Patients were treated daily and patients rated their pain on a Likert scale each day before treatment. **Results**: The alternative therapy employed in this study showed an average pain reduction of 72.1%. There was a 77% average pain reduction in patients with HZ onsets of more than one year and a 68% reduction in patients with HZ onsets between one month and one year. Almost two-thirds of the 56 PHN patients reported pain reductions of between 75 and 100% **Interpretation** These data, although preliminary, appear to suggest that alternative therapy provide good pain relief for most patients presenting with PHN That patients with HZ onset of more than one year had greater average pain reduction than those with onset of less than one year suggests that the treatment and not spontaneous remission often seen in acute HZ was responsible for their improvement. Controlled randomized trials are now being conducted to validate the effectiveness of this therapy in the treatment of PHN

AM2

THE PREVALENCE AND PATTERN OF USE OF COMPLEMENTARY AND ALTERNATIVE THERAPIES IN PATIENTS WITH PROSTATE CANCER ON WATCHFUL WAITING. J. P.H. Ly, L. Klotz, N. Fleshner. **Department of Urology, Sunnybrook Health Science Centre, Canada, M4N 3N5**

Purpose: This study determines the prevalence and the pattern of use of complementary therapies among men with prostate cancer who are participating in an observational watchful waiting program and to identify demographic factors that are predictive to the consumption **Materials and Methods:** A cross-sectional anonymous survey was sent out to all participants in the TSRCC watchful waiting program This survey consisted of 10 questions related to complementary and alternative therapies Descriptive statistics were used to determine the prevalence and pattern of use of complementary therapies Proportions among different age ranges and levels of education were compared using the chi-square test with SPSS All hypothesis testing was 2-sided with 95% confidence **Results:** Of the 152 surveys sent out, 108 patients responded for a total response rate of 71% Thirty-seven percent of the patients reported the use of some form of complementary therapies The prevalence of usage of alternative therapies, special diets, and vitamins or minerals were 28%, 9% and 23% respectively The use of vitamins or minerals differed significantly among patients with various levels of education ($p = 0.012$) An increased usage was observed in patients who had a higher level of education The prevalence of use of special diets increased with younger age ranges ($p = 0.003$) Seventy percent of those who used complementary therapies had consumed vitamin E **Conclusion:** A significant proportion of patients in our watchful waiting program was not truly watchful waiting A number of them were using complementary therapies This poses great difficulty in conducting a randomized clinical trial on the effects of nutrients in this population

Anesthesia

AN1

EFFECT OF O_2 ON CEREBRAL BLOOD FLOW IN CO-POISONED SUBJECTS J Rucker*, J Tesler, A Takeuchi, B Greenhouse, A Vesely, S Kobrossi, R Somogyi, E Prisman, D Preiss, G Volgyesi, S Iscoe, A Slutsky, L Fedorko, J A Fisher Department of Anaesthesia, University of Toronto, Toronto, Canada M5G 2C4

Background: Initial treatment for CO poisoning consists of 100% O_2. However, because hyperoxia increases ventilation and decreases PCO_2 (*J Appl Physiol* 81:1683-90, 1996), cerebral blood flow (CBF) decreases. We hypothesized that maintaining normocapnia during O_2 inhalation would, compared to breathing 100% O_2, prevent a fall in CBF **Methods:** Fifteen healthy subjects (8 M, 7 F) were exposed to 1000 ppm CO in air to a carboxyhemoglobin concentration ([COHb]) of ~10% on two separate days. After each CO exposure, each subject breathed, in random order, either 100% O_2 or ~98% O_2 while maintaining normocapnia without rebreathing. Minute ventilation (VE), $FETCO_2$, and middle cerebral artery blood velocity (CBV) (an index of CBF) were recorded continuously. We periodically measured [COHb] from peripheral venous blood

	% Change from control (mean ± SE)	
	100% O_2	Normocapnic O_2
VE	+16 ± 8*	+74 ± 9*
$FETCO_2$	-10 ± 2*	0 ± 1
CBV	-5 ± 2*	+2 ± 2

*$p<0.05$ vs. control

Results: See table. Half-time of elimination of COHb was 59 ± 3 min for O_2 and 45 ± 2 min for normocapnic O_2 ($p<0.001$) **Discussion:** Maintaining normocapnia during O_2 treatment prevented a fall in CBF in all subjects, thereby increasing cerebral O_2 delivery. Furthermore, there is a decrease in half-time of elimination of COHb as a result of the increase in ventilation The standard treatment for CO poisoning, administration of 100% O_2, can be improved with a simple circuit to maintain normocapnia

AN2

PREVENTION OF HYPOXEMIA FOLLOWING CARDIAC SURGERY WITH REPEATED VITAL CAPACITY MANEUVER JA Tan* F Day, J Karski, G Djaiani, J Carroll, DCH Cheng Department of Cardiac Anesthesia, Toronto General Hospital University of Toronto, Toronto, Ontario, Canada

Introduction: Postoperative atelectasis and hypoxia remain common and serious problems in patients undergoing cardiopulmonary bypass (CPB) A variety of techniques to reduce atelectasis post CPB have been attempted, but no benefits have been demonstrated This prospective randomized controlled trial will investigate whether repetitive vital capacity maneuvers (VCM) reduces postoperative hypoxemia following CPB **Methods:** Following Internal Review Board approval we recruited 33 patients undergoing elective cardiac surgery Subjects were randomized to receive either two VCMs (on termination of CPB and on transfer to the ICU) (VCM group), or to act as a controls group Subjects in the VCM Group received a sustained lung inflation to 35cm H_2O for 15 sec (FIO_2=0.4) at separation from CPB and a further inflation of 30 cm H_2O for 5 sec on transfer to the ICU Both groups received routine ventilation (tidal volume 10cc/kg, FIO_2 0.5, peep 5cmH_2O, 10 breaths/min) A-a gradients and intrapulmonary shunt were compared between both groups at baseline, post CPB, ICU arrival and extubation **Results:** Results are expressed as mean ± 95% confidence intervals

SHUNT %	VCM (n=17)	Control (n= 16)
Baseline	13.7 (12.4-15.1)	11.6 (9.9-13.4)
Post CPB	14.0 (12.0-16.0)	16.2(13.9-18.5)*
ICU	10.2 (7.2-13.2)	9.2 (7.1-11.3)
Extubation	8.5 (7.0-10.0)	8.1 (6.0-10.2)

There was no difference in demographic data between the two groups There was a significant increase in shunt fraction in the control group following separation from CPB (*P=0.006 using paired t-test) This deterioration in shunt fraction did not occur in VCM patients prior to separation from CPB Both groups showed spontaneous resolution in shunt during the postoperative period

Conclusion: This preliminary study indicates that VCM maneuver prevents intrapulmonary shunt immediately post CPB This may prevent postoperative atelectasis and facilitate recovery in patients undergoing CPB

BC1

PHOSPHORYLATION OF RGS4 BY MAP KINASES ERK1 AND ERK2: A NEW REGULATION LINK BETWEEN G PROTEIN COUPLED RECEPTORS AND RECEPTOR TYROSINE KINASES Aleixo Muise* and Harry P. Elsholtz, Department of Laboratory Medicine and Pathobiology, Banting and Best Diabetes Centre, Faculty of Medicine, University of Toronto, TO, ON.

Members of the RGS (Regulator of G protein Signaling) protein family function as negative regulators of heterotrimeric G protein signaling by interacting with specific Gα subunits and enhancing GTP hydrolysis. The coexpression of RGS protein genes and their overlapping Gα specificity in single cell types has prompted studies into the regulation mechanisms of these GTPase activators. Although selective phosphorylation provides one attractive mechanism of regulation, covalent modification of RGS proteins has not yet been described. Our initial Western blot analysis of RGS4 (an RGS protein enriched in brain, heart, pancreas, and cell lines of pituitary and adrenal origin) revealed a 'doublet' migration pattern indicative of phosphorylated and dephosphorylated forms. In vitro kinase experiments using recombinant RGS4 and extracts from PC12 cells, showed phosphorylation of RGS4 but not of the control RGS protein GAIP. Inhibitor studies suggested that RGS4 might be phosphorylated by members of the MAPK family, which was directly confirmed using various immunopurified MAPKs. In-gel kinase assays showed that the MAPKs ERK 1 and 2 were the specific RGS4 kinases in PC12 cells. Interestingly, antibodies directed toward ERK1/2 coimmunoprecipitated dephosphorylated RGS4, while antibodies directed toward RGS4 also coimmunoprecipitated dephosphorylated MAPK. Moreover, in vitro GTPase assays showed that phosphorylation of RGS4 reduced its activation of Gα GTPase activity. To determine if hormone regulation would effect RGS4/MAPK association, PC12 cells were treated with growth factors (insulin, EGF, and NGF) which activate MAPK in either a transient or a sustained fashion. Coimmunoprecipitation of RGS4/MAPK complexes was found to correlate inversely with the duration of the MAPK response to these factors, further supporting a model in which phosphorylation of RGS4 precedes dissociation from a MAPK complex. This data provides evidence for phosphorylation as a novel mechanism of RGS protein regulation and points to a mechanism of cross-talk between two critical signaling pathways, namely G protein and MAPK.

BC2

SYNTHESIS AND SPECTRAL PROPERTIES OF A NOVEL CA^{2+} AND DIVALENT CATION SENSITIVE FLUORESCENT PROBE. Peter K. Stotland*, Samuel Dougaparsad, Jae Kim, and Sergio Grinstein Programme in Cell Biology, The Hospital for Sick Children, University of Toronto, M5G 1X8

It is well established that the fluorescent probe fura-2 shows a spectral response upon binding Ca^{2+} that enables changes in intracellular free Ca^{2+} concentration to be determined through fluorescence ratio imaging. Fura-2 coupled to particles, such as zymosam or latex beads, would allow for the measurement of Ca^{2+} within specific compartments of the degradative pathway in phagocytic cells. However, the chemical properties of fura-2 have prevented efficient coupling to particles. Here we describe the synthesis and spectral properties of a fura-2 derivative-coupled particle, zymosam-FF6. Using a 2-step synthesis, the FF6 fluorescent probe was covalently linked to zymosam particles. Spectral analysis of zymosam-FF6 in the absence of Ca^{2+} revealed an excitation peak at 380 nm, while emission was monitored at 510 nm. Upon binding Ca^{2+}, zymosam-FF6 exhibited an absorption shift towards the u.v. range with an excitation peak at 340 nm. The addition of divalent cations such as Fe^{2+}, Zn^{2+}, and Mn^{2+} quenched excitation causing decreased fluorescence intensity at 340 nm. Thus, we have developed a probe that will enable us to describe changes in both Ca^{2+} and various divalent cation concentrations by employing fluorescence ratio imaging. More importantly, given the fact that the FF6 fluorescent probe is covalently linked to a zymosam particle, we will be able to perform measurements of Ca^{2+} and divalent cation concentrations at definitive stages of the degradative pathway in phagocytic cells.

BC3

CARBACHOL INHIBITS cAMP-DEPENDENT CHLORIDE SECRETION AND Na/K/2Cl COTRANSPORT VIA A PROTEIN KINASE C MECHANISM. V. Tsai, J. Song, J.B. Matthews. Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Carbachol(CCH) is a cholinergic agonist which activates Ca^{2+} dependent pathways including protein kinase C (PKC). In T84 human intestinal epithelial cells, CCH was shown to acuvate a novel PKC isoform, PKCε without activating the conventional isofrom PKCα. In contrast, phorbol myristate acetate (PMA) is known to activate both PKCα and PKCε. PMA inhibits cAMP-dependent intestinal chloride secretion and disrupts membrane integrity. We found that CCH, which acts upstream of PMA, mimics the PMA induced inhibition of intestinal chloride secretion but does not induce the concomitant disruption of membrane integrity. Here, we explain the discordant effects of CCH and PMA using inhibitors of different PKC isoforms. METHODS: T84 human intestinal epithelial monolayers were grown on permeable supports. The cAMP-dependent changes in short-circuit current (I_{sc}) and electrical resistance were measured by voltage-current clamp. Monolayers were pretreated with or without the conventional PKC isoform inhibitor Go6976 (1mM) or the conventional and novel PKC isoform inhibitor Go6850 (1mM) and then treated with or without CCH (100uM) or PMA (100nM) in the basolateral chamber prior to stimulation with the cAMP agonist forskolin (10uM). RESULTS: 4 hours CCH treatment inhibited forskolin-induced I_{sc} by 66.7 +/- 1.8 % (n=3,p<0.0005). This is comparable to previously reported PMA inhibition of forskolin-induced Isc. CCH had no effect on resistance, while 4 hours of PMA dropped resistance by 26.4 +/- 1.2 % (n=5, p<0.0001). Gö6850 abolished both PMA and CCH inhibition of Isc, but Go6976 did not. Gö6976, however, prevented the PMA induced drop in resistance. CONCLUSION: CCH inhibits cAMP mediated Cl secretion but has no effect on epithelial resistance and membrane integrity. This contrasts with PMA which inhibits Cl secretion and damages membrane integrity. This data suggests that CCH acts through PKCε isoforms to inhibit I_{sc} without affecting PKCα whereas PMA acts through both PKCα and ε to inhibit I_{sc} and decrease membrane resistance.

CV1

ROLE OF NON-INVASIVE CARDIAC TESTING IN PREDICTING CARDIAC RISK AFTER KIDNEY-PANCREAS (SPK) TRANSPLANTATION

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Coronary artery disease is commonly associated with end-stage renal failure in patients with diabetes, and is a leading cause of morbidity and mortality after SPK transplantation. The pre-transplant assessment of cardiac risk usually involves several non-invasive investigations including myocardial perfusion scintigraphy (exercise or pharmacological stress) and gated radionuclide angiography. However, there is considerable controversy regarding their accuracy in determining significant coronary artery disease. This study was designed to test the hypothesis that these investigations do not predict adverse cardiac outcomes in patients who receive SPK transplantation.

The SPK transplantation program at the Toronto General Hospital was initiated in November 1995 and as of July 1999, 49 transplants have been performed. Clinical and scintigraphic data was collected prospectively in all SPK patients. In addition, formal cardiac evaluations were routinely repeated every year following transplantation. The major clinical outcome variables analyzed were mortality and major cardiac morbidity including unstable angina, myocardial infarct, arterio-coronary bypass and percutaneous transluminal coronary angioplasty. All patients were considered to have a low risk for cardiac morbidity based on the results of their preoperative evaluation.

Overall, 28 of the 49 patients did not have cardiac events. Eight patients had 12 events before transplantation; 9 patients had 12 events after transplantation; and 4 patients had events both before and after transplantation. Three patients died, two of which were vascular related. Formal statistical analyses are currently being performed to determine the predictive value of pre-operative testing. However, our data clearly shows that despite the use of routine cardiac testing, the prevalence of cardiac morbidity was high after SPK transplantation

CV2

AUTOLOGOUS HEART CELL TRANSPLANTATION IMPROVES INFARCTED PORCINE HEART FUNCTION

Alex Kulik*, Gilbert Tang*, Ren-Ke Li, Terrence M Yau, Donald A G Mickle, Richard D Weisel Division of Cardiac Surgery, Toronto General Hospital, University of Toronto, Canada

Objective Transplantation of fetal rat cardiomyocytes into scarred rat heart has been previously shown to improve heart function However, the allografted cells were rejected despite cyclosporin therapy We therefore evaluated the effects of transplantation of autologous heart cells into infarcted porcine heart

Methods A myocardial infarction was created in 17 adult pigs by occlusion of the distal left anterior descending artery with an intraluminal coil Myocardial biopsies were obtained from the left ventricular septum at the time of infarct creation, and heart cells were isolated and cultured *in vitro* for 4 weeks Four weeks after infarction, echocardiography showed a dyskinetic anterorapical region and a SPECT MIBI scan showed minimal perfusion and very few viable myocytes in the infarct zone A left thoracotomy was then performed and either autologous cells (transplanted, N=11) or culture medium (control, N=6) were injected into the infarcted region Four weeks after transplantation, the SPECT MIBI scan was repeated, followed by baseline and caval occlusion measurements of ventricular pressure and volume using Millar and conductance catheters The transplanted and control hearts were then examined histologically

Results SPECT MIBI scanning demonstrated a significant increase in left ventricular ejection fraction at 4 weeks after cell transplantation compared to pre-transplantation, indicating improved contractility Left ventricular preload recruitable stroke work (PRSW) and end-systolic elastance were significantly greater in the transplanted hearts than in the controls ($p<0.05$), indicating better systolic function Tau (a measure of the early, active relaxation phase of diastole) and the slope of the end-diastolic-pressure-volume relation (a measure of the passive diastolic properties of the left ventricle) were not different between the transplanted and control groups Histological studies showed that transplanted heart cells formed visible cardiac tissue within the myocardial scar There was no evidence of rejection of the transplanted heart cells

Conclusions Autologous heart cell transplantation improved the function of infarcted porcine heart Cell transplantation may become a novel therapeutic option for patients who have congestive heart failure following a myocardial infarction

CV3

FUNCTIONAL CONSEQUENCES OF CALCYCLIN EXPRESSION IN RAT MYOCARDIUM. A C Nevin*, J.N Tsoporis, A Marks, T.G Parker. Department of Medicine, University of Toronto, Canada

End-stage cardiac disease and the accompanying sympathetic hyperactivity, may lead to hypertrophy resulting in the expression of fetal genes e.g. skeletal alpha actin (skACT), beta myosin heavy chain (βMHC) as well as members of the S100 family of calcium binding proteins. The S100 proteins have been implicated as effectors in calcium-mediated signal transduction pathways including cell growth and proliferation We have recently shown that S100β is part of an intrinsic pathway that limits the hypertrophic response. To define a role for calcyclin (S100A6), the induction of calcyclin and physiologic consequences of this induction were explored in both animal and culture models of cardiac hypertrophy respectively Calcyclin, absent in adult rat heart, was induced in several models of cardiac hypertrophy including rat coronary artery ligation, mouse aortic banding, and following norepinephrine infusion into rats, as detected by RNase protection assay A full-length cDNA of the human calcyclin gene was co-transfected into cultured neonatal rat myocardial cells along with chloramphenicol acetyltransferase reporter plasmids containing the promoters of the skACT, βMHC, or αMHC genes. Following transfection, contractile gene expression was determined in response to diverse trophic agents including adrenoceptor agonists. T3, angiotensin II, prostaglandin $F_{2\alpha}$, tumour necrosis factor α, and fetal bovine serum. Trophic stimulation induced the skACT and βMHC promoters approximately 1.5-2.5 fold T3 stimulated the αMHC promoter approximately 1.5 fold Co-transfection with calcyclin inhibited the induction of skACT, βMHC, and αMHC by the various growth factors These results taken together demonstrate that expression of calcyclin in chronic cardiac hypertrophy plays a possible role as a negative regulator of contractile gene expression.

CV4

THE ROLE OF THE TRANSIENT OUTWARD CURRENT AND ACTION POTENTIAL PROFILE IN MODULATING EXCITATION-CONTRACTION COUPLING IN RAT VENTRICULAR MYOCYTES. Rajan Sah*, Roger Kaprielian and Peter H. Backx. *Departments of Medicine and Physiology, University of Toronto*

Prolongation of the action potential is a common finding of heart disease, typically as a result of reductions in repolarizing transient outward currents (I_{to}). Action potentials are prolonged within 48 hours following left anterior descending (LAD) artery ligation in rat hearts due to reductions in I_{to}. The reductions in I_{to} were also associated with decreases in the expression of the K^+ channel genes, Kv4.2 and Kv4.3, both of which are known to encode I_{to} in adult heart. Our previous studies, both in a transgenic mouse overexpressing the Kv4.2N subunit and in the rat LAD ligation model, show that action potential prolongation due to a reduction in I_{to} results in a near doubling of the peak systolic calcium transient. Furthermore, consistent with the presence of prolonged action potentials and elevated intracellular calcium levels, early stage transgenic hearts are hypercontractile as assessed by echocardiographic and hemodynamic measurements In this study we examined the underlying mechanisms responsible for elevated $[Ca^{2+}]_i$ transients in response to I_{to} reduction. Rat ventricular myocytes stimulated with a train of long action potentials (recorded from a post MI rats) show a 2.6-fold elevation of $[Ca^{2+}]_i$ transient amplitude and a 4.8-fold augmentation of unloaded cell shortening relative to myocytes stimulated with a short action potential (derived from sham operated rats) Under conditions of equal SR Ca^{2+} load, achieved by using 8-10 conditioning pulses with a 100 ms duration, long post MI APs still resulted in a more than 2-fold increase in $[Ca^{2+}]_i$ transients and a 4.7-fold increase in cell shortening relative to short control APs.

These results suggest that the elevated $[Ca^{2+}]_i$ transients following changes in AP profile originate almost exclusively from changes in the efficiency of Ca^{2+} release from the SR and not from changes in SR Ca^{2+} load. Indeed, at low SR Ca^{2+} loads, achieved using a train of short APs, both short and long AP triggers resulted in calcium transients and cell shortening that were nearly identical to those observed at high SR loads (long AP train). In conclusion, large changes in excitation-contraction coupling can occur as a result of I_{to} reductions as occurs in hypertrophic and diseased myocardium These changes appear to be primarily linked to indirect effects of AP alteration on L-type Ca^{2+} current

CV5

THE MYTH OF SIMPLICITY IN ADULT SUBAORTIC STENOSIS. Keith Tsoi*[1], Glen S. Van Arsdell MD[1], William G. Williams MD[1], David A. Harrison MD[2], Tirone E. David MD[2]
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Discrete subaortic stenosis in the adult has often been viewed as a simple but unusual problem. The natural history following operative therapy is not well defined because results have generally been incorporated with reports on all age groups. This paper focuses on 45 adult patients ages 22 years to 78 years (median 44) having subaortic stenosis not due to hypertrophic obstructive cardiomyopathy. Operations were performed between November 1975 and December 1998. Follow up evaluation ranges from 3 months to 22.6 years (mean of 9 years). In the surviving patients, five (16%) have been reoperated or scheduled for reoperation. Eight patients (18%) have doppler peak outflow gradients over 30 mm Hg. Ten patients (26%) have documented left ventricular hypertrophy, and 2 patients (6%) have moderate or severe aortic insufficiency. Current status indicates 15/45 patients (33%) have or will require aortic valve replacement. This report demonstrates the need for complex reconstruction in 53% of cases with discrete subaortic stenosis. 33% require aortic valve replacement, and 29% have required more than 1 operation. It is a myth that discrete subaortic stenosis in the adult is a simple disease.

Clinical Pharmacology

CP1

ORAL VERSUS RECTAL ACETAMINOPHEN DOSING IN FEBRILE CHILDREN. E. Lavine*, D. Scolnik, N. Young, M. Rezvani et al Divisions of Emergency Services, Clinical Pharmacology and Toxicology, Paediatrics, and Pharmacy, The Hospital for Sick Children, University of Toronto, Canada, M5G 1X8.

Background: Although evidence has accumulated to support a need for increased dosage of acetaminophen when administered in rectal suppository form, many of these studies have not been published in English, nor have they been properly designed or applicable to children. Recommended North American dosage remains 15 mg/kg acetaminophen in both oral and rectal form for the treatment of fever. It is important to determine the appropriate rectal dosage needed to attain adequate serum levels and effective defervescence.
Purpose: To determine if 15 mg/kg PR acetaminophen is as effective as 15 mg/kg PO, and if 30 mg/kg PR demonstrates a greater effect on reducing fever.
Methods: 89 febrile children were randomly assigned to receive one of three acetaminophen treatments: 15 mg/kg PO, 15 mg/kg PR, or 30 mg/kg PR. Children were between the ages of 6 months to 6 years, presented with rectal temperature ≥39° C, and had received no acetaminophen in the previous 4 hours. Primary outcome measure was change in rectal temperature, and secondary outcome measures were i) plasma concentrations of acetaminophen as indicated by salivary levels and ii) acceptability of dosing route as measured by parental response on linear scale.
Results: No significant difference was seen in a 3-group comparison of area-under-curve (AUC) for temperature over time (ANOVA, p=0.689). Analyses of salivary concentration data and parental acceptance of route are currently being performed.
Conclusions: 15 mg/kg PR acetaminophen may yield equal defervescence to 15mg/kg PO, and further increases in PR dosage may not have significant effect. Further conclusions depend upon completed data analysis.

CP2

PREGNANCY OUTCOME FOLLOWING GESTATIONAL EXPOSURE TO CLOMIPHENE CITRATE: A PROSPECTIVE CONTROLLED STUDY. R A B Soniani*, Darren Katz, Shinya Ito MD Motherisk Program Division of Clinical Pharmacology & Toxicology, Hospital for Sick Children University of Toronto Canada

Clomiphene citrate has been demonstrated to be a useful therapy for female infertility caused by anovulation. No human data exist about the inadvertent gestational exposure of clomiphene citrate and pregnancy outcome. The objective of our study was to determine if clomiphene citrate exposure during pregnancy is associated with higher risk of birth defects. Methods: A prospective cohort study with control. All pregnant women counseled by the Motherisk program (a Teratogen Information Service) on the risk of clomiphene citrate exposure during pregnancy were followed prospectively using a standard questionnaire. Cases were matched for age, gravidity, cigarette smoking and alcohol consumption with 32 control women unexposed to any known teratogens. The primary outcome was the incidence of major malformations as defined by the Centre of Disease Control (CDC). Results: A total of 28 pregnant women were exposed to clomiphene citrate during pregnancy. The rates of major malformations in the clomiphene citrate group (8%) did not differ significantly from controls exposed to non-teratogens (3%) (N = 41, relative risk = 2.54, 95% confidence interval 0.24 to 26.48). Conclusions: This first human report on inadvertent gestational exposure to clomiphene citrate suggests that clomiphene citrate is not associated with an increase risk of major malformations.

CP3

THE IMPACT OF ADVERSE DRUG EVENTS ON SUBSEQUENT THERAPY IN PATIENTS INITIATING HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) , E.Yeung*, E. Phillips, S. Gardner, K. Leeb, A. Rachlis, & N. Shear, Dept. of Clin. Pharmacology & Infectious Diseases, Sunnybrook & Women's Health Sci. Ctr., Univ. of Toronto & the HIV Ontario Observational Database, Toronto, Ontario, Canada

Adverse drug events (ADEs) are common in people living with HIV. The impact of ADEs to antiretroviral agents on the use of "optimal" treatment regimens, as defined by current consensus guidelines, is unclear. Using the HIV Ontario Observational Database (HOOD) and the Ontario Drug Distribution and Monitoring Program (ODDMP) we did a retrospective cohort study to look at ADEs as a possible risk factor for changes in treatment and subsequent suboptimal antiretroviral therapy (SOT). Chi-square test was used to examine categorical variables and student t-test for continuous variables, with significance level set at 0.05. A total of 259 patients were identified who were initiated on HAART ("optimal therapy") between November 1995 and July 1998 and had at least two 6 month follow-ups. 100 (38.6%) out of 259 patients had an ADE associated with HAART at some point during the period of observation. The mean number of HAART regimens used in patients coded as having ADEs on HAART was 2.52 versus 1.89 in the group without ADEs ($p<0.001$). Patients developing an ADE while taking HAART were significantly more likely to subsequently receive SOT (55% versus 29.6% of those with no ADEs, $p<0.001$). Specific ADEs associated with SOT were: allergic and cutaneous reactions ($p<0.001$), neuropathy ($p=0.008$) and hematologic toxicity ($p=0.02$). Gastrointestinal side effects were not associated with SOT ($p=0.18$). There was no association between non-drug related adverse events, baseline CD4+ or viral load, CDC class, race, gender and mode of HIV transmission and SOT. In conclusion, in patients initiated on optimal therapy (HAART), ADEs are associated with both increased exposure to different antiretroviral agents and subsequent time spent on SOT. Since both of these factors potentially affect long-term outcomes prospective data to define this effect as well as guidelines for antiretroviral therapy in the setting of specific ADEs will be essential in the successful management of these patients.

Dermatology

DE1

META-ANALYSIS OF THE CLINICAL ACCURACY OF DERMATOLOGISTS AND PRIMARY CARE PHYSICIANS IN DIAGNOSING MELANOMA E Weil*, S Chen, D M Brayata, I Olkin Department of Dermatology, Stanford University, USA 94305

A principal role of primary care physicians (PCPs) is to regulate referral to specialists, such as dermatologists This system is subject to question in the case of malignant melanoma, because early diagnosis is particularly crucial to a favourable outcome We were, therefore, interested in determining (1) how accurately PCPs and dermatologists diagnose melanoma, and (2) how well they recognize the need for biopsy or referral in lesions suspicious for melanoma To answer these questions, we conducted a comprehensive search of MEDLINE, CANCERLIT, and Embase using the following MeSH subheading and keywords: *melanoma, diagnosis, screening, misdiagnosis, physician, primary care, family practice/practitioner, general practice/practitioner, internist, internal medicine, dermatologist,* and *skin specialist* Additionally, bibliographies of selected articles, Science Citation Index, and conference proceedings were searched In total, 566 titles were surveyed and 159 full articles were reviewed Studies were included in the meta-analysis if they reported sensitivity of melanoma diagnosis or problem lesion recognition Thirty-four studies were included in the meta-analysis Data from different studies were combined in three ways: Effect sizes (the difference between dermatologist and PCP sensitivities) were combined using a fixed-effect model to estimate an overall effect size; summary odds ratios of dermatologists versus PCPs were calculated using the Mantel-Haenszel fixed-effect model, and sensitivities were combined to give an overall diagnostic sensitivity per physician group Analysis showed that dermatologists have a 13% higher sensitivity rate in diagnosing melanoma The summary odds ratio for a correct melanoma diagnosis by dermatologists versus PCPs was 4 46(95%CI 2 63-7.56), and the summary odds ratio for correct biopsy/referral decision was 1 96(95%CI 0 92-4 16) The overall sensitivity of melanoma diagnosis was 0 996 for dermatologists and 0 81 for PCPs The overall sensitivity of the biopsy/referral decision was 0 95 for dermatologists and 0 82 for PCPs. This analysis of the literature demonstrates that dermatologists are superior to PCPs in the diagnosis and initial management of melanomas This finding supports the view that PCPs should have a low threshold for referral of suspicious lesions, and direct access to dermatologists for examination of pigmented lesions should be considered

Endocrinology

EN1

MONOUNSATURATED FATTY ACID DIETS IMPROVE GLYCEMIC CONTROL THROUGH INCREASED SECRETION OF GLUCAGON LIKE PEPTIDE-1. *Antonio Rocca[1]*, Jonathan LaGreca[1] and Patricia Brubaker[1,2]*
Departments of Physiology[1] and Medicine[2], Faculty of Medicine, University of Toronto

Diets enriched in monounsaturated fatty acids (MUFAs) benefit glycemic control Furthermore, MUFAs stimulate secretion of the antidiabetic hormone Glucagon-Like Peptide-1 (GLP-1) *in vitro* To determine whether the MUFA-induced benefit in glycemic control was due to increased GLP-1 release, lean Zucker rats were fed a synthetic diet containing 5% fat derived from either Olive Oil (OO, 74% MUFA) or Coconut Oil (CO, 6% MUFA) for 2 wk. Food intake and body weight were similar for both groups over the feeding period The OO group had improved glycemic tolerance as compared to the CO group in both oral and duodenal glucose tolerance tests (AUC 121±61 vs 290±24 mM·120min, $P<0.05$, 112±28 vs 266±65 mM·120min, $P<0.05$, respectively) This was accompanied by increased secretion of gut Glucagon-Like Immunoreactivity (gGLI, an index of GLP-1) in the OO rats as compared to the CO rats (402±96 vs 229±33 pg/ml at t=10min, $P<0.05$) To determine the total contribution of GLP-1 to the enhanced glycemic control, the GLP-1 receptor antagonist exendin$^{9-39}$ (Ex^9) was infused 3 min prior to a duodenal glucose tolerance test This abolished the benefit in glycemic control conferred by OO feeding and resulted in a deterioration of glycemic control in the OO+Ex^9 group when compared to the OO controls (AUC 331±21 vs 112±28 mM·120min, $P<0.05$) This was partially due to increased release of glucagon with Ex^9 To probe the mechanism by which the MUFA diet improved GLP-1 secretion, an *in vitro* model of the GLP-1-secreting L cell was incubated for 24 h in the presence of either 100µM oleic acid (MUFA) or 100µM palmitic acid (Saturated FA) and subsequently challenged with Glucose-dependent Insulinotropic Peptide (GIP), a known stimulator of the L cell Pre-exposure to oleic acid increased GIP-induced GLP-1 secretion when compared to controls (178±14 vs 132±9 pg/ml, $P<0.01$). However, palmitic acid pre-exposure abolished GLP-1 secretion induced by GIP In conclusion, these results demonstrate that the benefit in glycemic control obtained with MUFA diets is the result of increased GLP-1 secretion through a mechanism of enhanced L cell sensitivity These results suggest that diet therapy with MUFAs may benefit the treatment of impaired glucose tolerance through increased GLP-1 secretion

HD1

THE EFFECT OF VERTICAL ACCESS ON EMERGENCY MEDICAL SERVICE RESPONSE TIME. Mark P. Angelini*, Dr. B. Schwartz, Dr. L.J. Morrison
Division of Prehospital Care, Department of Emergency Medicine, Sunnybrook and Women's College Health Sciences Centre, Faculty of Medicine, University of Toronto, Canada, M4N 3M5.

Objectives: To determine: 1) if the time interval between ambulance arrival at the scene to paramedic arrival at the patient ("vertical response" time interval) in high-rise buildings is significantly longer than in houses; 2) the barriers encountered by paramedics in responding to emergency calls in high-rise apartment buildings; and, 3) the effect of barriers to paramedic access to patients on this time interval.
Methods: A prospective, single blinded, observational study. An independent third-party observer collected time intervals on emergency medical service (EMS) calls. Potential barriers impeding EMS access to patients were recorded.
Results: The median vertical response interval for 42 calls was 109 seconds (interquartile range, 76.5 to 198.5 seconds) and represents 25% if the total EMS response time. Vertical response time for emergency calls originating from apartment buildings (n=17) were significantly prolonged in comparison to those from houses (n=10) (median 198.5 seconds vs. 79 seconds, $p<0.001$. The median vertical response interval for apartment buildings where EMS calls originated $\leq$ 2 floors above ground was 157.5 seconds (137.3 to 215.5 seconds). The most common barriers encountered were the need for an entry code to enter the building (88.2%) and the elevator was too small to fit stretcher in prone position (82.4%). In potentially life-threatening (delta priority), median vertical response interval times in apartment buildings (n=6) were significantly longer than in houses (n=6) (218.5 seconds to 80.0 seconds), $p<0.001$
Conclusions: The vertical response interval represents a significant component of the total EMS response time and is significantly longer for calls onginating in apartment buildings. Barriers impeding paramedic access to patients significantly prolong this interval. The increased response time due to vertical access significantly impacts on time to treatment in the highest priority calls where delay has been shown to effect outcome.

HD2

INFORMED CONSENT IN HEAD AND NECK SURGERY: MEASURING THE EFFECTIVENESS OF AN EDUCATIONAL INTERVENTION. Y. Chan*, J.C. Irish, L.E. Rotstein, O. Mostafchi, D.H. Brown, P.J. Gullane, S.J. Wood
Department of Otolaryngology/Surgical Oncology, Princess Margaret Hospital, University Health Network, University of Toronto, Toronto, Canada

Informed consent is an essential component of clinical practice. Previous studies have demonstrated that the recall rate immediately after the interview was 41%, and steadily declined to 35 to 57% at seven days and 16% at six months after the initial session. In a former study, the effectiveness of the informed consent process in head and neck surgery was evaluated and results showed that the average patient recall rate of potential surgical complications was only 48%. This prospective study was designed to examine the effects of an educational intervention, in the form of written information, on patient knowledge and recall of possible risks from parotidectomy or thyroidectomy. Sixty consecutive patients seen at an academic tertiary care centre were randomized into either an educational intervention or a control group. At the preoperative visit, both groups received a verbally delivered checklist of risks specific for the surgery to be performed during the routine consent process. The educational intervention group was also given an information pamphlet with written information accompanied by graphic illustrations, in addition to the verbal checklist. The effectiveness of the educational intervention was determined by comparing the rate of risk recall between the intervention and control groups. Rate of recall was also correlated with various demographic parameters including patient age, gender, level of education, Occupation as well as the length of time from the consent interview to the recall interview was also taken into consideration. The overall risk recall rate from both procedures is 40.5%. The recall rate of the intervention group was determined to be 52.8% compared to 29.9% for the control group ($p<0.05$). Results demonstrated that the recall rate was higher in all the intervention groups when patients were stratified into various gender, age, education level categories. In summary, patients' ability to recall potential risks was significantly increased by an educational intervention.

HD3

MEDICAL COMMUNICATION WITH DEAF PATIENTS AND ITS IMPACT ON QUALITY OF HEALTH CARE DELIVERED AND RECEIVED. D.W. Cheng*, M. Fulford. Faculty of Medicine, University of Toronto, Canada, M5G 1X8.

Background: Accurate communication between physicians and patients is critical to providing effective medical care. Without access to interpreters, communication between physicians and the deaf may be ineffective. Currently, there is no legislation obligating the Ontario government to provide professional sign interpreters to the deaf in medical settings. Therefore, deaf Ontarians are being denied equal access to public services such as Universal Health Care. Additionally, communication barriers between physicians and the deaf may result in a lower quality of health care. **Objectives:** To determine: 1) if the deaf are less satisfied than the hearing with the quality of their health care; 2) if patient-physician communication is a barrier preventing the deaf from receiving the best medical care; 3) if communication is a barrier, whether the physician's level of knowledge about Deaf culture is a contributing factor, and 4) what physicians can do to improve the quality of health care for the deaf. **Methodology:** Three confidential surveys were developed based on a literature search. Self-administered written surveys and cross-sectional American Sign Language interview-administered surveys were conducted with deaf persons (n=26) at Bob Rumball Centre for the Deaf, North York, Ontario, and Ontario Association of the Deaf. Self-administered written surveys were completed by hearing persons (n=31) and Toronto-area physicians (n=8). The pilot data from all three surveys were summarized using descriptive statistics. Differences between hearing and deaf groups with respect to demographics, health care utilization, perceptions of health care, and health knowledge were tested using χ^2 tests for differences in proportions and t-tests for differences in means. Additionally, the potential confounding effects of age, gender, and education on health care knowledge was investigated by multiple linear regression. **Results:** The deaf are less satisfied than the hearing with the quality of their health care ($p<0.05$), and patient-physician communication is a barrier preventing the deaf from receiving the best medical care (61%). Contributing factors are inadequate access to sign interpreters and physicians' level of knowledge about Deaf culture. **Conclusion:** Access to and quality of health care for the deaf would be improved with better access to interpreters and education of physicians on Deaf culture.

HD4

RECOMMENDATIONS AND COST ANALYSIS OF A UNIVERSAL NEWBORN HEARING SCREENING PROGRAM IN ONTARIO. T.A. Chin*, C. Chalin, K. Riko, M. Hyde. Otologic Function Unit, Mt. Sinai Hospital, University of Toronto, Canada, M5G 1X5

While it is widely accepted that unmanaged congenital hearing loss can lead to significant problems in language and social development, no programs in Ontario universally screen for this condition. Yet, the availability of new tools for screening newborn hearing suggests that early identification of hearing loss may now be practically and economically feasible. The purpose of this project was to review the recommendations, costs and benefits associated with the implementation of a universal newborn hearing screening program in Ontario. A literature search using MEDLINE resulted in the review of 45 relevant articles regarding universal newborn hearing screening. These articles included position statements from various US and European agencies, all of which recommended identification and intervention of hearing loss within the first few months of life. Further articles reported results from universal newborn screening programs already in operation, the strong majority supporting such programs and reporting earlier ages of diagnosis and intervention of hearing loss through cost-effective screening methods. Using reported prevalence and performance data from universal newborn hearing screening programs in Rhode Island and Colorado, projected estimates for a hypothetical screening program in Ontario were calculated. Out of 135,150 infants born in Ontario from July 1, 1997 to June 30, 1998, a universal screening program in Ontario would have identified between 286 to 408 infants with congenital hearing loss. Projections from a cost effectiveness analysis of Colorado results suggest that early identification of these children alone might have saved Ontario residents up to $7,923,814 in heath care and educational costs over a 12 year period. If Ontario achieved 100 percent universal screening with complete follow-up, then a one year program might have potentially identified up to 851 children with hearing impairment, saving up to $22,485,930 over a 12 year period. These results suggest that it could be beneficial in several ways for Ontario to implement universal newborn hearing screening. A more detailed cost analysis taking into account Ontario's unique characteristics would be informative.

HD5

PHYSICIAN SURVEY TO ASSESS WILLINGNESS TO PARTICIPATE IN OR TO SUPPORT A RANDOMIZED TRIAL (RCT) OF HORMONE REPLACEMENT THERAPY (HRT) AFTER A DIAGNOSIS OF BREAST CANCER (BC). ME Del Giudice*, CA Sawka, KI Pritchard, HA Llewellyn-Thomas, ME Trudeau, J Lewis, E Franssen. Toronto Sunnybrook Regional Cancer Centre, Department of Medical Oncology, Faculty of Medicine, University of Toronto, Canada, M4N 3M5.

Premature menopause is common among younger women treated with adjuvant therapy for breast cancer. The impact of short and long term adverse effects of estrogen deficiency on quality of life and survival have become prominent concerns for these women. Based on a theoretical increased risk of recurrence, HRT is relatively contraindicated in women after BC. A physician survey has been completed to determine physician willingness to participate in or to support an RCT of HRT after BC. METHODS: A self-administered survey was mailed to a cross-section of 1900 Canadian medical, radiation and surgical oncologists, gynecologists and family physicians. Willingness to participate in or to support an RCT of HRT after BC was asked. Knowledge and attitudes towards clinical trials and HRT for well women and after BC were also assessed. RESULTS: Overall 538 (37%) of eligible physicians responded. 78% reported that they would be willing to refer a woman after BC to an RCT of HRT versus placebo. Rates of referral ranged from 58% among family physicians to 84% among medical oncologists (p=0.001). Using multivariate modelling, the factors that significantly predicted participation included: overall support of HRT after BC (p=0.0001) and in well women (p=0.04); support of clinical trials (p=0.0001), ongoing BC trials are conducted at their institution (p=0.003); if ongoing RCTs in well women show beneficial results (p=0.015); and they currently prescribe HRT to women after BC (p=0.027). Physicians would be more likely to refer women with a low risk of recurrence, node negative, > 2 years post diagnosis and estrogen receptor negative. CONCLUSIONS: An RCT of HRT after BC is feasible among Canadian physicians. However, educational interventions describing evidence from small studies of HRT after BC and the adverse effects on quality of life resulting from ovarian dysfunction secondary to adjuvant therapy may be needed. Beneficial results from large RCTs in well women may be required to increase acceptability of such a trial

HD6

Title Page: Development and Validation of a Quality of Life Questionnaire for Patients with Pituitary Adenoma

Peter Kan, Michael Cusimano, M.D. Ph. D. Division of Neurosurgery, St. Michael's Hospital, University of Toronto.

Abstract:

Objective. To develop and validate a self-administered questionnaire for measuring the health-related quality of life (HRQOL) of patients with pituitary adenoma

Methods. Literature review and focus group interviews with 9 patients, 2 family caregivers, 2 RNs, and a neurosurgeon were used to develop the 106 item content of questionnaire Version 1.0. This questionnaire was mailed to 20 patients, and the 30 most important items ranked by the patients with 17 additional items considered important by health care professionals, constituted Version 2.0 of the questionnaire

For validity and reliability assessment, Version 2.0 was mailed to 55 patients Concurrent validity was assessed by Pearson correlation coefficients between subscales of Version 2.0 and both the RAND36 and the Karnofsky Scale Version 2.0 scores in extreme groups defined by the Karnofsky scores were compared by a T test Test-retest reliability, a month apart, was determined by the Pearson correlation coefficient and a T test between the two sets of scores.

Results. 47 patients (85.5%) returned completed Version 2.0 Concurrent validity for each of the subscales were: General Health (0.62), Physical Function (0.78), Social Functioning (0.52), Emotional Well-Being (0.62), and the Karnofsky Scale (0.75). Extreme groups were significantly different (15.66, 23.12, $p = 0.011$) Test-retest reliability ($n = 24$) was 0.88. Scores 1 month apart were not significantly different (21.42, 20.68, $p = 0.73$). Patients recommended that 7 items be dropped from Version 2.0.

Discussion/Conclusions. A patient-centered HRQOL questionnaire developed for patients with pituitary adenoma was shown to have good evidence for validity and reliability.

HD7

ASSESSMENT OF FEEDING PATTERNS IN MEDICAL-SURGICAL ICU-A PROSPECTIVE STUDY

K K. Kundhal*, P S. Kundhal, M S. Herridge, A M. Cheung. Toronto General Hospital, University of Toronto, Canada.

Background. As few studies have been conducted to monitor feeding patterns in the ICU, there is a need to address whether feeding regimens are being administered with compliance to established recommendations.

Methods. We conducted a descriptive prospective study assessing the feeding patterns of ICU patients admitted over a 6 week period (n=61) in a single institution. As some patients were admitted twice during the study, certain statistics were based on the number of independent ICU admissions* (n=68). Data retrieval forms were created to determine patient demographics, time from date of admission to initiation of therapy (feeds (FD) or TPN)*, days on therapy*, and total TPN or FD administered.*

Results. Average age of the 61 unique patients (41M/20F) admitted was 61±18 y [20-95]. 7 patients were admitted twice during the study. Length of stay in the ICU was 6.4± 7.2 d[1-31]* with patients being followed until death (n=14), discharge (n=43) or end of study (n=11). Time to initiate FD (n=25) and TPN (n=11) were 2.8±2.6d [0-8]* and 3.1±3.2d [0-10]*. The number of days patients remained on therapy was 9±7d [1-27]* for FD and 6±4d [1-15]* for TPN. Total amount of FD and TPN administered to patients was 8119±9658 ml [70-36610]* and 5997±4524 ml [1012-15646]*. FD types included Isosource (n=14)*, Novasource (n=12)* and Jevity (n=6)*. 6 patients were fed both FD and TPN, with 2 starting on FD and 4 on TPN.

Conclusion. Evidence suggests that patients are initiated on nutritional therapy earlier than recommended. Further definitive studies are needed to assess whether this is occurring on a larger scale and to explore rationale for such practice.

* - denotes statistics based on independent ICU admissions

HD8

IS THE NEUROLOGIC AND ADAPTIVE CAPACITY SCORE (NACS) A RELIABLE METHOD OF NEWBORN EVALUATION? Malik N*, Halpern S, Littleford J, Brockhurst N, Owen H, Youngs P, Liolli A Department of Anaesthesia, University of Toronto, Canada

INTRODUCTION The NACS is a multifactor scale used to assess the effects of medications administered to the mother during the delivery process on normal term newborns It consists of twenty items organized into two scales, adaptive capacity and neurological assessment Despite being used worldwide for over sixteen years, its reliability has never been assessed This study was undertaken to assess the reliability using internal consistency and interobserver variability

METHODS The study involves two independent observers assessing normal term newborns. Observers underwent a systemic training process to ensure that different observers scored responses consistently The population being assessed consists of term newborns within 2 hours of birth (normal, cephalic delivery) The interobserver reliability will be calculated using intraclass correlation coefficient (ICC) and 95% confidence interval (An ICC> 6 is fair correlation, an ICC>.8 is excellent correlation) Cronbach's α will be calculated to determine internal consistency The sample size of the study is 200 newborn infants

RESULTS Recruitment is ongoing

DISCUSSION A reliable test is needed for assessment of the newborn who may be exposed to intrapartum medications The NACS has been used for this purpose without having its reliability assessed If the NACS is found to be a reliable scale, validity studies should be carried out If not, the NACS should not be used for the assessment of the newborn and a new scale should be developed

HD9

EVALUATION OF THE EFFECT OF THE QUESTION PROMPT SHEET ON QUESTION ASKING BEHAVIOUR, SATISFACTION WITH PATIENT-PHYSICIAN COMMUNICATION, DECISION-MAKING PREFERENCES, ANXIETY AND PSYCHOLOGICAL ADJUSTMENT IN WOMEN WITH BREAST CANCER. J.L. Surette*, BBA, T. Bunston, PhD; D.Stewart, MD; R. Deber, PhD
Women's Health Program, University Health Network, University of Toronto, Canada, M5G 2C4

Background: Women with breast cancer need accurate information to understand their illness, make decisions and cope with distress. Since patients prefer obtaining information from their physicians, interventions have been designed to improve physician-patient communication.
Hypothesis: The 17-item Question Prompt Sheet (QPS) will facilitate information exchange. Women given the QPS will ask more questions, will be more satisfied with their physician, will engage in more shared decision making, will be less anxious and have greater psychological adjustment to cancer. (PAC)
Methods: 101 women with newly diagnosed breast cancer were randomized to either the experimental group (n=51), which received the QPS prior to their initial oncology visit, or the control group (n=50) which did not. The Problem-Solving Decision-Making Scale, the State-Trait Anxiety Inventory and PAC Scale were completed by the patients pre/post visit. The Patient-Doctor Interaction Scale and QPS evaluation were completed post visit. The consultations were audiotaped.
Results: Of patients using the QPS, 78% perceived it facilitated question asking and 50% perceived they asked more questions than usual. However, the QPS did not affect standardized outcome measures of satisfaction with physician, decision-making, anxiety, or adjustment to cancer.
Conclusion: Results show that the QPS is highly regarded by the women as they perceive it facilitates asking more questions. Analysis of the transcripts of the audiotaped consultations is required to determine if the QPS objectively affects question asking behaviour.

Health in the Community

HC1

VISION SCREENING IN INNER CITY TORONTO SCHOOL CHILDREN – PART II. G. Ahuja*, C. Chalin, J. Chapman, D. Wong. Department of Ophthalmology, St. Michael's Hospital, University of Toronto, Canada.

Vision is integral to learning for children. Currently there is no systematic programme for screening visual problems in school-aged children. In the past, the Board of Health, in cooperation with the Board of Education, conducted regular visual screening in schools. This service is no longer provided.

This study identified visual problems in an inner city school population and the need for regular screening of school-aged children. The study was conducted at Rose Avenue Public School which is located in the St. James Town area of Toronto. The school has the highest ESL (English as a Second Language) rate in the city (83%). The area is home for an increasing number of new Canadians and low income families with children.

Parental consent was obtained to screen all Grade 3 and 6 students in the school and administer a brief questionnaire about home and school issues. A single trained individual utilized a Snellen Eye Chart under controlled standardized conditions. A total of 177 students were tested and interviewed.

Of the 177 students tested, 47 had poor visual acuity (below 20/30 on the Snellen scale), 75% had never had their eyes tested and only four wore prescribed glasses. Approximately half the children lived in an apartment with more than one family in it. Classrooms were crowded (over 30 students per teacher). Demographics of the area point to high unemployment, poverty and few social resources. Further research on screening for vision problems in inner city school children is being developed.

HC2

BARRIERS TO APPROPRIATE DIABETES MANAGEMENT AMONG HOMELESS PERSONS IN TORONTO. A.L. Bugeja, S.W. Hwang, Inner City Health Program, St Michael's Hospital, University of Toronto.

Homeless persons with medical illnesses may face many obstacles to appropriate health care and disease management. This study identifies barriers to appropriate diabetes management among homeless adults in Toronto and examines the adequacy of diabetic control in this population.

Persons with a known diagnosis of diabetes who were staying at any homeless shelter for single adults in Toronto were eligible for this study. Potential participants were identified by shelter staff and by random sampling of shelter residents. Factors affecting diabetes management were assessed using a structured personal interview. Glycemic control was assessed on the basis of hemoglobin A1c levels.

We identified 60 homeless persons with diabetes, of whom 50 completed an interview. The majority of participants were men (82%) and had type 2 diabetes (86%). The average age was 50 years (range, 23 to 75 years), and diabetes had been diagnosed for an average of 7 years (range, 2 weeks to 36 years). Most individuals (80%) were being seen regularly by a family doctor or specialist for their diabetes. Treatment for diabetes was oral agents in 62%, insulin in 28%, and diet alone in 8% of subjects.

Most participants (72%) stated that they were experiencing difficulties in managing their diabetes. Qualitative analysis of these reports revealed 3 predominant themes: nutritional, personal, and logistic. Most notably, 64% felt that the diet provided at shelters was unsuitable for persons with diabetes. Logistic problems related to the storage and retrieval of insulin, diabetic supplies, or food were reported by 18%. Personal or stress-related issues were cited by 8% as interfering with their ability to manage their diabetes. Hemoglobin A1c levels (measured in 48 individuals) were <0.075 in 25% (optimal control), 0.075-0.091 in 31% (sub-optimal control), and >0.091 in 44% (inadequate control).

We conclude that most homeless persons with diabetes encounter significant barriers to appropriate diabetic management and have inadequate glycemic control. Changes in the shelter system may alleviate problems related to nutritional and logistic issues. Most homeless persons with diabetes have a regular source of medical care, which may represent an important avenue for intervention in this population.

HC3

COMPARISON OF THE QUALITY OF LIFE OF PATIENTS WITH DIFFERENT ETIOLOGIES OF ERECTILE DYSFUNCTION R. Bitar*, S. Herschorn and A. Glazer. Division of Urology, Sunnybrook and Women's College Health Sciences Centre, University of Toronto, Canada, M4N 3M5.

We postulated that the health of men with erectile dysfunction (E.D.) after radical prostatectomy (R.P.) would be better than those whose erectile dysfunction is due to other etiologies since men after R.P. may be physically healthier and more able to deal with their E.D than those with other etiologies. Thus, the purpose of this study is to compare the quality of life of patients with different etiologies of erectile dysfunction, in order to assess any differences.

All new patients referred to the E.D. clinic over a 3 month period were assessed with the Duke Health Profile, a validated self-administered questionnaire that assesses six health measures (physical, mental, social, general, perceived health and self-esteem) and four dysfunction measures (anxiety, depression, pain and disability). 162 patients were studied, with 18.5% of the patients having their E.D due to R.P. The average age of the patients was 58.3 years.

R.P. patients had higher health measure scores and lower dysfunction scores than the others. The perceived health scores of radical prostatectomy patients were significantly higher that the others, whereas their pain and disability scores were significantly lower than the rest ($P<0.05$). The differences in the physical and general health scores were reaching statistical significance.

We conclude that men who have E.D. due to a radical prostatectomy have a higher perceived health, and less pain and disability on a quality of life assessment than men whose erectile dysfunction is due to other etiologies. Their physical health and general health appear to be better than the others.

HC4

HEREDITARY BREAST CANCER: AN INFORMATION SHEET FOR PATIENTS D.W. Cheng*. Faculty of Medicine, University of Toronto, Canada, M5G 1X8

Background: Approximately 82-90% of women in the general population are interested in genetic testing for their susceptibility to breast cancer; however, less than 5% are at high risk for hereditary breast cancer and meet current referral criteria for genetic testing. Additionally, current genetic testing can only identify mutations to the Breast Cancer 1 and Breast Cancer 2 genes, which are responsible for 50-60% of all hereditary breast cancer cases. Many women with a family history of breast cancer will visit their family physicians seeking clear, understandable information on genetic testing. The role of the family physician includes assessing breast cancer risk, providing basic information on genetics and cancer, counseling high-risk patients on genetic testing, and assisting in dealing with implications of test results. Potential challenges to family physicians fulfilling their role include limited knowledge of a rapidly changing field and time constraints. **Objectives:** To develop an information sheet for patients in the family practice setting that provides basic information on hereditary breast cancer and indications for genetic testing. **Methodology:** A literature search using the Medline database was performed for the period January 1995 to February 1999 using the MeSH headings (1) Genetic Screening, (2) Genes, BRCA1 (3) Breast Neoplasms/[Genetics], (4) Decision Making, and (5)Counseling. Based on a review and synthesis of the literature, the need for a patient information sheet on hereditary breast cancer was identified and the requirements of such a sheet were defined. **Results:** A patient information sheet was designed to: (i) provide basic knowledge on genetics and genetic testing; (ii) explain the role of genetic mutations in hereditary breast cancer; and (iii) inform patients when genetic testing is appropriate. The sheet was written: (i) to target laypersons in a family practice setting; (ii) to provide sufficient detail to educate the patients; and (iii) in a user-friendly format. The information provided in the sheet was useful to patients of all risk levels; however, the scope was limited to omit information that would be provided to high-risk patients by familial cancer clinics. **Conclusions:** An information sheet was developed to help provide the basic knowledge necessary to understand hereditary breast cancer and genetic testing, inherently complex topics. The sheet benefits the patient and physician by informing the patient, easing the demands on the family physician, and supplementing physician-patient discussions.

HC5

ANALYSIS OF HEAVY USERS TO THE EMERGENCY DEPARTMENT AT A LARGE URBAN HOSPITAL. K. Dang*, M.A. Mycyk, H.J. Ovens. Division of Emergency Services, Mount Sinai Hospital, University of Toronto, Canada, M5G 1X5.

Objective: The literature suggests that repeat visitors are a small segment of the emergency department (ED) population that consumes a disproportionately high quantity of emergency services with little health benefit. Our objective was to examine the medical and social profile of this population at Mount Sinai Hospital.

Methods: The hospital database was searched to identify "heavy users," who made 10 or more visits to the ED in the fiscal year 1997/98. A retrospective chart review of heavy users was done to collect demographic, medical, and social data.

Results: 21 727 patients (54.5% female) made a total of 28 135 visits to the ED. Of these, 36 (41.7% female) were identified as heavy users and made 505 visits. Six of the patients were considered to be heavy users in the preceding fiscal year and another six in the following fiscal year; only one patient was a heavy user in all three years. The mean number of visits per patient for the total ED population was 1.3 and for heavy users was 14.0. The mean age of the total ED population was 46.6 years and of heavy users was 49.2 years. The proportion of admitted patients for the total ED population was 12.9% and for heavy users was 9.3%. Of the 36 heavy users, 35 charts were reviewed; one chart was missing. A family physician was identified for 74.3% of heavy users, and a psychiatrist was identified for 37.1%. A chronic medical condition was identified in all heavy users: psychiatric only 37.1%; psychiatric co-morbidity 14.3%; and somatic only 48.6%. A psychiatric condition was identified as the primary reason for ED visit in 19.4% of heavy users and in 4.9% of the total ED population. Among the heavy users, 30.8% used alcohol, 23.1% used drugs, and 31.4% used narcotics. A socioeconomic review revealed that 69.9% were single, 48.5% had no fixed address, 24.2% lived alone, and 64.0% were retired or unemployed.

Conclusions: Compared to similar studies, the number of heavy users at Mount Sinai Hospital and their impact on emergency resources were lower. However, the heavy user profile, characterized by chronic medical and social problems, substance abuse, and low socioeconomic status, was consistent with these studies. Quality of care will be further assessed in a focussed chart review of select patients.

HC6

A COMPARISON OF TWO GENERIC QUALITY OF LIFE MEASURES ACROSS A BROAD SPECTRUM OF MS PATIENTS P. S. Giacomini*, T. Gray and P. O'Connor. Multiple Sclerosis Clinic, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada, M5B 1W8

OBJECTIVE: To determine which of two popular generic quality of life (QoL) measures correlates better with disability in MS and whether stratification by E.D.S.S. score has any bearing on these correlations.

BACKGROUND: Patient QoL is an important consideration in deciding appropriate treatment measures for patients with a chronic illness. In MS, the costly major therapies involve regular injections that may, despite beneficial therapeutic effects, have a negative impact on patient QoL.

DESIGN/METHODS: Cross-sectional study of 53 MS patients with E.D.S.S. ranging between 0 and 9. The participants were administered two different generic QoL surveys, the utility based Health Utility Index III (HUI3) and the profile based Short Form-36 questionnaire (SF-36). The results from these instruments were compared to one another, patient demographic variables and E.D.S.S. scores.

RESULTS: Of the 53 patients, 38 had relapsing remitting multiple sclerosis (RRMS) and 9 had secondary progressive multiple sclerosis (SPMS). The remaining 6 patients included 5 with primary progressive and 1 with progressive relapsing MS. Overall, 27 had mild (E.D.S.S. score 0 – 3), 18 had moderate (E.D.S.S. score 3.5 - 6.5) and 8 had severe disability (E.D.S.S. score 7 - 9). Stratified by E.D.S.S. score, those with mild disability showed a highly significant correlation ($p<0.001$) between E.D.S.S. and both QoL measures (Physical Composite Score (PCS) of SF-36 $r = -0.810$ and HUI3 $r = -0.735$). Conversely, in the moderate to severe groups, correlations between E.D.S.S. and QoL measures were poor and non-significant (for moderate: PCS of SF-36 $r = 0.155$, HUI3 $r = -0.144$, and for severe: PCS of SF-36 $r = -0.067$, HUI3 $r = -0.273$).

CONCLUSION: Both the PCS of the SF-36 and the HUI3 correlate significantly with E.D.S.S. in mild disease. However, as disease severity increases, both the PCS of the SF-36 and the HUI3 correlate poorly with E.D.S.S., indicating they may be subject to limiting floor effects. This emphasizes the potential utility of a more disease specific QoL instrument, that is not subject to the same floor effects, in assessing QoL of MS patients with more advanced disease.

HC7

PRESIDENTIAL PROSPECTS: LONG-TERM SURVIVAL OF DISTINGUISHED MEDICAL STUDENTS. JC Kwong*, DA Redelmeier. Department of Medicine, Sunnybrook and Women's College Health Sciences Centre, University of Toronto, Canada, M4N 3M5.

Being elected president of a medical school class is a distinctive event that signifies popularity, ambition, and success. We studied whether this early measure of personal achievement was associated with a decrease in life-time all-cause mortality.

We selected all class presidents from the University of Toronto Medical School who graduated between 1900 and 1998. For each individual, we then selected the student appearing alphabetically before and alphabetically after the president in the graduating class photograph. Deaths were obtained by consulting the obituaries of the Canadian Medical Association Journal, the College of Physicians and Surgeons of Ontario, and alumni publications. A total of 1497 physicians were found, the median duration of follow up was 51 years, and 573 deaths were identified. Kaplan-Meier estimates indicated that survival after medical school was 5.2 years shorter for presidents than for other graduates (50.9 vs 56.1, $p<0.005$). This corresponded to a 28% increase in death rates (95% confidence interval 8 to 52). Adjustment for graduation era, sex, and race yielded similar findings (95% confidence interval 11 to 57). Analyses based on just those known to be dead showed a 23% increase in death rates (95% confidence interval 4 to 47). Similarly, specialty training post-graduation was also associated with a 20% increase in death rates (95% confidence interval 0 to 40). In contrast, staying in Toronto for one's career was associated with no increase in death rates (95% confidence interval –12 to 12).

We suggest that distinctive early personal achievement signifies characteristics that lead to shortened survival in physicians.

HC8

AN EXAMINATION OF ALL-CAUSE MORTALITY IN OSCAR WINNING ACTORS AND ACTRESSES. S.M. Singh*, D. Redelmeier. Clinical Epidemiology Unit, Sunnybrook & Women's College Health Science Centre, University of Toronto, Canada, M4N 3M5

Background: Winning an Academy Award is a great international honor that can elevate the status of a performer for a long time. We examined whether this increase in socioeconomic status was associated with a subsequent reduction in mortality of Academy Award winners.

Methods: We identified all actors and actresses ever nominated for an Oscar in either a leading or supporting role. For each nominee, we identified another performer who was a cast member in the same film, had the same sex, and was born in the same era. Individuals were then classified as a Winner, Nominee or Unknown.

Results: A total of 1626 performers were analyzed. Life-expectancy was 3.8 years longer for Winners than for Unknowns (79.5 vs 75.7, $p=0.004$). This was equal to a 27% relative reduction in death rates (95% confidence interval 9 to 41). Similar results were obtained after adjusting for birth era, sex, and race. Additional Oscars won were associated with a further 21% relative reduction in death rates (95% confidence interval 4 to 35). Additional nominations offered no significant reduction in death rate and other additional films in the performer's career also offered no significant reduction in mortality.

Conclusion: Winning an Academy Award is associated with a substantial gain in life expectancy for actors and actresses. This gain is not easily explained by fundamental demographic and occupational characteristics of these individuals. Given this, the public's tremendous adoration and emulation of outstanding stars is not completely irrational.

Immunology

IM1

ANTI-MHC IMMUNE RESPONSES IN BOTH MICE AND MACAQUES INDUCED BY PLASMID DNA IMMUNIZATION IN THE CONTEXT OF A NOVEL HIV-1 VACCINE APPROACH. CS Dela Cruz*, JW Chamberlain, KS MacDonald & BH Barber. Institute of Medical Science, Faculty of Medicine, University of Toronto, Ontario, Canada.

Major histocompatibility complex (MHC) proteins are known to be incorporated into HIV-1 envelope as the virion buds from the host cell surface. Studies using SIV infection of macaques have demonstrated that immunization with uninfected human cells or purified HLA proteins alone can provide protection from challenge with live infectious SIV when it is grown in human cells expressing the same MHC alleles. This represents one of the few examples of sterilizing immunity conferred by any HIV-1 vaccine thus far. The induction of immune responses to non-virally encoded antigens, specifically to the *MHC proteins*, represents an important option to consider with respect to vaccine design against HIV-1 for humans.

Here we examined plasmid DNA immunization strategy as a better alternative to cellular or protein immunogens for the induction of xenogeneic and allogeneic anti-MHC immune responses. These studies were conducted in C57BL/6 mice and HLA-transgenic mice, respectively. We also examined similar strategies in rhesus and cynomolgus macaques. In the mouse models, we compared the immunogenicity of HLA-A2- and HLA-B27-expressing splenocytes with the corresponding plasmid DNA immunogens. Results from the transgenic mouse experiments indicated that immunization with either class I and class II MHC-encoding DNA vectors elicited strong antibody responses recognizing conformationally intact MHC molecules. Our data also show that immunization with class I MHC-encoding DNA immunogens induced potent cytotoxic T-lymphocyte responses that are able to kill chromium-labeled MHC-expressing targets.

Immunization of the non-human primates (i.e. macaques) with human MHC-encoding plasmid DNA induced xenogeneic anti-MHC antibody responses *in vivo*, while vaccinating macaques with DNA encoding allogeneic-MHC from a different non-related macaque elicited allogeneic anti-MHC antibodies production. All these immunization studies in different animal species show that immunization with MHC-encoding DNA vectors can effectively be used to induce specific anti-human MHC immune responses in both HLA transgenic and non-transgenic mice, and specific anti-macaque allogeneic MHC immune responses in macaques. These findings demonstrate the potential use of DNA vaccines to mobilize both antibody and cell-mediated anti-MHC immune responses in humans, as part of a new alternative/complementary strategy in HIV-1 vaccine design.

IM2

Effect of Human Leukocyte Antigen Type on Perinatal HIV-1 transmission in Non Breast Fed Infants of the Women and Infant Transmission Study (WITS)

Matukas, Larissa M.*; Rustam, TP*; Luscher, MA*‡; Shearer, WT*, Hillyer, GV§, King, SM£, Landay, AL¶; and MacDonald, KS*†.
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Human leukocyte antigens (HLA) are responsible for presentation of peptides of foreign and self proteins for cellular immune recognition. HLA Class I or Class II restricted T cell effector responses against HIV-1 viral antigens are thought to contribute to protection against HIV infection. For example, studies of exposed uninfected infants and adults by ourselves and others, have shown that class I and class II restricted cytotoxic T cell (CTL) and T helper responses respectively can be detected. In addition, alloimmune responses (vigorous responses mediated by the recognition of foreign HLA molecules) have been recognized as a defense against HIV and other retroviruses in a number of model systems. The protection is thought to stem from immune responses to HLA molecules on the surface of HIV infected cell, and to HLA molecules incorporated into the envelope of viral particles.

As part of the Women and Infant Transmission Study (WITS), a multicentre study including the most demographically representative sample of racial and socioeconomic populations affected by HIV across North America, we have undertaken to examine the correlation between HLA type of the mother and child and HIV transmission. The WITS design is a cohort study designed with allocation based on the maternal viral load. Cellular DNA has been isolated from EBV-transformed lymphocytes of study members. In the present work, a nested case control design from the cohort study, HLA class I type has been determined from isolated DNA by sequence specific polymerase chain reaction. Correlation with a number of variables will be determined, including occurrence of viral transmission, such as mode of delivery and time of rupture of membranes. Results will be discussed.

Infectious Disease

IM3

SHP-1 MODULATION OF CD19 TYROSINE PHOSPHORYLATION IS MEDIATED THROUGH DEPHOSPHORYLATION/DEACTIVATION OF THE LYN PROTEIN TYROSINE KINASE. Ally-Khan Somani*, Fenhao Xu, Xuewen Song, Jinyi Zhang and Katherine A. Siminovitch, Departments of Medicine, Immunology, Molecular and Medical Genetics, University of Toronto and the Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario, M5G 1X5, Canada.

SHP-1 is a SH_2 domain containing cytosolic tyrosine phosphatase implicated in the downregulation of signaling cascades coupling the B cell antigen receptor (BCR) to cell proliferation. SHP-1 effects on BCR signaling appear to reflect its capacity to interact with and dephosphorylate several BCR comodulators including CD22 and FcγRIIB1. In view of our observation that CD19 tyrosine phosphorylation is constitutively increased in B cells from SHP-1 deficient motheaten mice, we investigated the possibility that CDI9 represents another BCR comodulator susceptible to SHP-1 dephosphorylation. However analysis of CD19 coimmunoprecipitable tyrosine phosphatase activity in CD19 immunoprecipitates from both motheaten and wild-type B cells and from SHP-1 immunodepleted wild-type cells revealed that SHP-1 accounts for only a minor portion of CD19 associated tyrosine phosphatase activity. In contrast, CD19-associated Lyn tyrosine kinase activity from both resting and BCR-induced B cells was found to be markedly increased in motheaten viable (me^v) compared to wild-type. In view of the important role for Lyn kinase in the phosphorylation of CD19, we investigated the influence of SHP-1 on Lyn. Herein we show that both constitutive and BCR-induced Lyn tyrosine kinase activity to be also markedly increased in me^v compared to wild-type B cells. The data also revealed association of SHP-1 with Lyn in BCR stimulated WEHI-231 cells and the capacity of Lyn to interact with the SHP-1 NH_2-terminal SH_2 domain *in vitro*. These data, together with cyanogen bromide cleavage data revealing the capacity of SHP-1 to dephosphorylate the Lyn autophosphorylation site (Y397), provide strong evidence that SHP-1 functions include the negative regulation of Lyn activation in B cells. Thus Lyn deactivation/dephosphorylation represents a likely mechanism whereby SHP-1 exerts its influence on CD19 tyrosine phosphorylation and, by extension, its inhibitory effect on BCR signaling.

ID1

INFECTIOUS COMPLICATIONS IN LIVER TRANSPLANT RECIPIENTS TRANSPLANTED FOR HEPATITIS C.

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Background: Patients transplanted for liver disease due to hepatitis C virus (HCV) may be at higher risk of infectious complications due to immunomodulatory effects of HCV viral replication post-transplant.

Methods: To assess this, we retrospectively analyzed infectious complications in 135 consecutive liver transplant recipients with HCV and compared it to 137 randomly selected controls who were transplanted for other diseases during the same time period.

Results: Patients with HCV did not differ significantly from controls with respect to age, sex and mean cyclosporin or tacrolimus levels at 7 days, 1 month, and 6 months post transplant. The incidence of acute rejection, steroid resistant rejection and use of anti-lymphocyte products was not significantly different between the two groups. Major infectious complications occurred in 34.1% (46/135) of patients who were transplanted for HCV vs. 18.2% (25/137) of other transplant patients (p=0.014). There was a significantly higher incidence of opportunistic infections (major fungal, cytomegalovirus, varicella zoster virus, and other) (34.1% vs. 18.2%, p=0.003) in HCV patients compared with other transplant patients. Major fungal infections occurred in 10.4% of HCV patients vs. 2.9% of controls, p=0.013) The incidence of minor infectious complications was also significantly higher in HCV transplant patients (31.1% vs. 18.2%, p=0.014) HCV transplant patients were also more likely to have recurrent episodes of both major and minor infections (3.74 episodes/patient vs. 2.14 episodes/patient, p<0.001) and (1.31 episodes/patient vs. 1.04 episodes/patient, p=0.015) respectively. There was no significant difference in the incidence of bacteremia between the two groups (24 1% vs 25.9%, p=NS).

Conclusion: HCV liver transplant patients have an increased incidence and increased episodes of infectious complications following transplant In particular, the incidence of opportunistic infections are increased among these patients after liver transplantation and more aggressive prophylaxis strategies may be warranted

International Health

IH1

THE EFFECTS OF REFORMS ON MATERNAL AND CHILD HEALTH CARE SERVICES IN ARMENIA **A.A. Kulidjian*, G. Aslanyan, D. Zakus. Faculty of Medicine, University of Toronto**

Armenia gained independence from the former Soviet Union in 1991. In 1995, the Ministry of Health initiated comprehensive health care reform to decentralize and change the financing of health services, and to enhance primary health care. As a result, it introduced a Basic Benefits Package (BBP) which, along with other services, includes prenatal care, delivery and postnatal care. The fee-for-service system was legalized in July 1997. Under the BBP, a pregnant woman has access to a specified number of prenatal care visits, free delivery in a hospital, and a specified number of visits to a pediatric clinic after giving birth. Additional visits and services have to be paid by the consumer. The purpose of this study was to evaluate the changes that have taken place in access to, utilization of, and satisfaction with maternal and child health services in Armenia after the introduction of comprehensive health care reform.

A survey was carried out among women who were selected for an interview according to the following criteria: they had delivered at least one of their children before the initiation of the health reforms in 1995, and one child less than six months prior to their interview Of the 206 women who met the criteria, 102 agreed to be interviewed. Among those interviewed, 87% used urban clinics for care and delivery, and 13% rural clinics The questionnaire measured the socio-demographic characteristics, prenatal history, and experiences with access to, utilization of, and satisfaction with prenatal, delivery and postnatal health care services

After the initiation of reforms, the number of visits to prenatal clinics has decreased from an average of 11 before 1995 to 9 during the last pregnancy ($p < 0.01$). The most common reasons were inadequate means to pay for services and difficulty in getting to a clinic. The length of time before the first visit to a prenatal clinic has increased from 12 weeks before the reforms to 14 weeks ($p < 0.01$) There has been no change in the level of satisfaction with prenatal services before and after the reforms Although hospital delivery is covered under the BBP, women report that it is difficult to obtain services without additional payment. Women seem more satisfied with the level of care they received during their last delivery compared to that before 1995 ($p > 0.05$). Women noticed no difference in postnatal maternal and child services

This study demonstrates that health care reforms in Armenia have decreased access to and utilization of maternal and child care services, with little or no effect on satisfaction with these services

IH2

ATTITUDES TOWARDS THE TREATMENT AND CARE OF PERSONS WITH AIDS IN JIMMA, ETHIOPIA. S.B. Wilton*, T.R. Harris, D. Zakus, H. Argaw. International Health Program, Faculty of Medicine, University of Toronto, Canada, M5S 1A8. Department of Community Health, Jimma Institute of Health Sciences, Jimma, Ethiopia.

BACKGROUND: The prevalence of AIDS is increasing exponentially in Ethiopia. Due to a lack of access to health care or effective anti-viral medications, persons with AIDS (PWAs) in Ethiopia often receive only rudimentary community care. Very little is known about the attitudes community members have towards these people and their care. We hypothesized that increased factual AIDS knowledge and personal contact with PWAs would be positively correlated with more empathic attitudes.

METHOD: An original cross-sectional survey investigating basic knowledge of AIDS, as well as attitudes towards the treatment and care of PWAs was developed. Questions were scored, so that knowledge and attitude levels could be compared with demographic factors. Trained Ethiopian health care workers, administered our survey, to health clinic attendees, health care providers, and Jimma Institue of Health Sciences students in July, 1998.

RESULTS: A total of 898 interviews were completed; 578 clinic attendees, 248 students, and 72 staff. Among clinic attendees, higher scores on knowledge and attitude questions were associated with young age, increased education and socio-economic status, urban residence, and previous contact with or care for PWAs. Among students and staff, AIDS knowledge was almost universally high, but attitudes varied substantially, with many of the same factors.

CONCLUSIONS: Gaps remain in AIDS education in Ethiopia, and factual AIDS knowledge does not necessarily overcome attitudinal biases against PWAs. Personal contact with, and experience with caring for, PWAs, is associated with more empathic attitudes towards them.

ME1

EDUCATING PHYSICIANS ABOUT EARLY INTERVENTION FOR YOUNG HANDICAPPED CHILDREN. E. Thompson, W. Roberts, A. Hong.* Child Development Centre, The Hospital for Sick Children, University of Toronto, Canada, M5G 1X8

Early Intervention for young children with handicapping conditions has been demonstrated to improve both child and family functioning. Early identification and provision for coordinated intervention is important to produce maximum positive outcomes for both child and family. In Ontario, Infant Development Programs provide this intervention. A survey of programs in Ontario, revealed that over 6000 children are currently receiving this service. 43% of the children seen by these programs were referred to intervention by physicians. Interventionists indicated that physicians often wait too long before making a referral. Few physicians use formal screening tools to determine the presence of developmental delays. 13 intervention programs provide training to medical students and medical residents. Data collected in the survey describes how this training occurs. Factors facilitating successful interaction between families, physicians and early interventionists and barriers that hinder that interaction are discussed. Interventionists pinpoint key information to be included in physician education.

ME2

STUDENT FEEDBACK IN PROBLEM-BASED LEARNING ACROSS FIVE ONTARIO MEDICAL SCHOOLS: HOW DO WE COMPARE AT THE UNIVERSITY OF TORONTO?

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Problem based learning (PBL) is now an integral part of medical curricula around the world. Although proper and timely feedback is an essential component of medical education[1], the types of feedback that students receive in PBL has not been systematically investigated. In the first multi-school study of PBL in Canada, we sought to determine the types of feedback (grades, written comments, group feedback, individual feedback from examiner, peer feedback, self-assessment, no feedback) that students receive in PBL. We surveyed a representative sample of 103 final year medical students in the five Ontario schools.

Students reported the amount of feedback (as percentage) according to type as follows

	Ottawa (n=18)	Queens (n=22)	McMaster (n=17)	Toronto (n=28)	Western (n=18)	Total (n=103)
No feedback	10%	13%	9%	14%	6%	11%
Mark/grade	64%	38%	4%	16%	65%	36%
Written	71%	63%	32%	32%	53%	49%
Group	71%	62%	78%	62%	78%	69%
Individual	81%	65%	65%	71%	68%	70%
Peer	54%	39%	83%	29%	64%	51%
Self	39%	27%	84%	28%	31%	39%

Across schools, students felt that the most helpful type of feedback in PBL was individual feedback from the examiner. From our data, it can be seen that individual feedback is one of the more common types of feedback given. Students also indicated a strong preference for peer feedback and group feedback. Unfortunately, peer feedback was not as widely reported in four of the five medical schools.

[1] Gil, D. Henis, M. and Jones P. Perceptions of medical school faculty members and students on clinical clerkship feedback. *Journal of Medical Education* 59 856-864 1984

ME3

CURRICULUM REFORM ACROSS FIVE ONTARIO MEDICAL SCHOOLS: WHAT HAS BEEN THE IMPACT ON FEEDBACK AND EVALUATION FROM 1992- 1999?

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In 1992, Hodges[1] looked at the different types of feedback received by 85 final year students in the 5 medical schools. They found significant differences in the types of feedback (grades, written comments, group feedback, individual feedback from examiner, peer feedback, no feedback) students received in different evaluation formats (written examinations, observed histories and physicals, clinical case reports, in-training evaluations, standardized patient interviews, and OSCE's). Since 1992, 4 of 5 Ontario medical schools have undergone curriculum renewal. It was anticipated that curriculum reform would lead to changes in the types of feedback students receive. This is the first study to compare the old and new curricula with respect to feedback and assess the relative importance that student learners place on these various types of feedback. In 1999, 103 final year students from the five Ontario schools were again surveyed using a similar instrument.

Evaluation modality	% of time no feedback received		Most common type of feedback	
	1992	1999	1992	1999
Written examinations	27	13*	MG (73%)	MG (90%)*
Observed history and physicals	10	12	IND (63%)	IND (70%)
Clinical case reports	24	21	IND (52%)	IND (62%)*
In-training evaluations	7	8	IND (54%)	WC/IND (77%)*
Standardized patient interviews	20	4*	IND (48%)	IND (71%)*
OSCE	27	5*	MG (51%)	MG (85%)*

MG = mark/grade, IND= individual feedback from examiner, WC = written comments * denotes $p<0.05$

Our results indicate (i) that students are receiving significantly more feedback in the areas of standardized patient interviews and OSCE's; (ii) in all areas the most common type of feedback given has not changed over the interval, but has increased in amount. The 1999 student cohort reported a preference for individual feedback from the examiner. As in 1992, there continued to be little use of self-assessment and feedback from peers in all evaluation modalities. Taken together, the results suggest an overall positive impact of curricular reform on feedback to medical students across Ontario.

1) Hodges, B., Brown, M., Norman, G., Richardson, D., and Turnball, J. The Effect of Feedback on Student Self Assessment during an OSCE. In: Rothman, A., and Cohen, R. Proceedings. The Sixth Ottawa Conference on Medical Education. Toronto, Ontario, Canada, June 26-29, 1994. Toronto, Ontario. University of Toronto Bookstore Custom Publishing. 1995

ME4

PHYSICIAN TRAINING IN ORGAN DONATION AND TRANSPLANTATION: THE IMPACT OF UNDERGRADUATE MEDICAL EDUCATION. J.B.Sacks*, S.Vohra, S.Shemie. Department of Critical Care Medicine, The Hospital for Sick Children, University of Toronto, Canada, M5G 1X8.

An imbalance persists between the demand for transplantation and organ availability, resulting in deaths on transplant waiting lists. Professional attitudes and knowledge remain underlying weaknesses contributing to poor donation rates in Canada.

We wish to evaluate the effectiveness of the undergraduate medical education in preparing physicians to address organ donation and transplantation with patients and families. Attitudes, beliefs, and knowledge of 1st year medical students will be initially assessed and subsequently compared in the same cohort of students at the end of the four-year curriculum.

A questionnaire was developed and administered to first year medical students at the University of Toronto. Of the 170 questionnaires distributed, 144 (85%) were completed. Despite 59% of respondents indicating a willingness to donate their own organs, only 40% have consented to donation on their driver's license; 29% of respondents remain undecided. Increased knowledge was cited as the predominant influence on attitudes toward organ donation. Family attitudes influence almost half of the respondents, yet 60% have yet to discuss organ donation with their family. Knowledge in the area of organ donation eligibility was relatively high despite lack of formal instruction. In contrast, knowledge of brain death and transplant survival rates was poor.

Preliminary data illustrates the variability of knowledge and attitudes in 1st year medical students and a separation between stated willingness and actual practice. A re-evaluation at the end of the fourth year curriculum will document changes over time.

MG1

INVESTIGATION INTO THE ROLE OF GENETIC VARIABILITY IN THE HUMAN IL-12 p40 AND IFN-ɣ GENES IN DETERMINING OUTCOME OF INFECTION WITH *P. FALCIPARUM.* S. Agrawal*, D. Kwiatkowski. University Department of Paediatrics, Oxford University OX3 9DU, UK.

Recent evidence suggests that variation between individuals in genes whose products control the immune response plays an important role in determining susceptibility to infectious diseases. In an attempt to explore this relationship in the context of malaria, we examined the extent of variation in the promoter region of the interleukin-12 (IL-12) p40 gene in an ethnically mixed group of healthy Gambian volunteers with the view of testing novel polymorphisms for association with severe malaria. A region of roughly 1.2 kb lying 5' to the start of transcription of IL-12 p40 was sequenced in 36 individuals using automated fluorescence technology. One polymorphism was found at a site –335 bp relative to the start of transcription, yielding an observed frequency of single nucleotide polymorphism of 1 in 43,800 and a normalized number of variant sites of 9.96×10^{-5}. This degree of genetic homogeneity represents a marked departure from the most comprehensive analysis of diversity in the non-coding regions of the human genome published to date, represented by a normalized number of variant sites of 5.30×10^{-4} (Lander *et al.*, Nature Genetics **22**), suggesting that the promoter region of IL-12 p40 may be under strong conservative selective pressure. The results of a screen of heterogeneous Gambian and Malawian samples for the –335 variant allele indicated that this allele was too rare to enable the detection of an association with severe malarial disease. A recently discovered polymorphism in the promoter region of interferon-gamma (IFN-ɣ), which is thought to follow IL-12 in the early immune response to infection with *P. falciparum*, was investigated for association with cerebral malaria or severe malarial anemia in a case-controlled study. Using ARMS-PCR, genotypes at this locus were established in over 300 Gambian children with cerebral malaria and/or severe malarial anemia and compared to those in 350 Gambian umbilical blood controls. After stratifying the analysis by mother's ethnic group, no significant differences were found between the proportion of individuals carrying the mutant allele in the control group compared to either of the disease groups. We conclude that there is as yet no evidence for association between polymorphisms in either the IL-12 p40 or IFN-ɣ genes and severe malaria.

MG2

SUBTELOMERIC FISH AND SKY DETECTS A CRYPTIC REARRANGEMENT IN A PREVIOUSLY UNDIAGNOSED CHILD

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Multiple congenital abnormalities and developmental delay in children can be caused by cryptic cytogenetic rearrangements in the subtelomeric regions. Current G-banding method is not ideal for detection of such rearrangements. Often the segment rearranged is small (<2 Mb), chromosomal ends are G-band light and G-bands of similar intensity are exchanged. FISH analysis is superior to G-banding for this purpose; however, checking for all telomeres one at a time is a labor intensive and costly process. A new FISH technique (Cytocell) screens all subtelomeric regions at the same time on one slide. The objective of this study was to assess the utility of this device in detection of subtelomeric rearrangements. The study was approved by the Research Ethics Board. Subjects were referred to the study by their physicians. Only those with normal G-banded karyotypes and either developmental delay, dysmorphic features, and/or multiple congenital anomalies were accepted. Using this method, an abnormal chromosome 5 was detected in a previously undiagnosed child with clinical features of trisomy 21 but with a normal G-banded karyotype (3 tests in 2 centres). The karyotype was determined to be 46, XY, der(5)t(5;21)(p13;q21.1). Results were confirmed by SKY and FISH using chromosome paints. Mother was found to be a carrier of a cryptic translocation between chromosomes 5 and 21: 46, XX, t(5;21)(p13;q21.1). This study suggests that subtelomeric FISH has a definite role for identifying rearrangements not detectable by G-banding. At the end of the summer, a second case with a subtelomeric abnormality was detected giving a detection rate of 2/6 unknowns (4 positive controls were used for technique validation). The study is ongoing.

MG3

MAP KINASE ACTIVATION DURING MOUSE EMBRYOGENESIS. George Zogopoulos* and Janet Rossant, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Canada.

Genetic experiments in mice have shown the importance of fibroblast growth factor (FGF) signaling in events of mouse gastrulation. However, it is not clear exactly which cells are receiving the FGF signal, nor whether FGF signaling is the only receptor tyrosine kinase pathway activated at gastrulation. Studies in Drosophila and Xenopus have shown that immunolocalization of phosphorylated MAP kinase can provide an accurate cellular readout of receptor tyrosine kinase function. We used this approach in wildtype mouse embryos to map the sites of MAP kinase activation. Wild type mouse embryos between day 6.5 and 9.5 of development were dissected and subjected to whole-mount immunocytochemistry with an anti-phosphorylated MAP kinase antibody. We observed increased immunostaining around the primitive streak (6.5-7.5dpc), while whole-mount immunostaining of later stage embryos (8.5-9.5dpc) revealed a diffuse pattern of MAPK activity. Interestingly, a role for FGF Receptor-1 (FGFR-1) in morphogenetic movement through the primitive streak has been previously demonstrated. In future investigations, we will employ the same approach to characterize MAPK activity in FGFR-1 -/- embryos. Comparison of the wildtype and FGFR-1 -/- patterns will elucidate the regions of MAPK activity that are dependent on FGFR-1 signaling. A better understanding of the complexities of growth factor signaling in development may provide new insights into normal development and differentiation, and may elucidate how disruptions in growth factor signaling cascades lead to congenital anomalies and diseases such as cancer.

MI1

THE IMPACT OF RETROSPECTIVE APPLICATION OF THE BI-RADS CRITERIUM ON THE POSITIVE PREDICTIVE VALUE OF FINE WIRE-EXCISIONAL BIOPSIES FOR BREAST CARCINOMA. C G Ball*, J K. MacFarlane, P. Chipperfield, M. Butchart Department of Surgery, St. Paul's Hospital, University of British Columbia, Canada, V6Z 1Y6

The American College of Radiology has recommended the Breast Imaging Reporting and Data System (BI-RADS) as the standardized scheme for describing all mammographic lesions. The purpose of this study was to assess the positive predictive value (PPV) of the mammographic features and final assessment categories defined in BI-RADS, as well as their potential use in further treatment selection.

A retrospective study was undertaken using patient files from January 1, 1994 to June 1, 1999 at St. Paul's Hospital in Vancouver, Canada. The mammographic features of 109 abnormal mammograms were used to assign final BI-RADS assessment categories (i.e. "probably benign", "suspicious", and "highly suggestive of malignancy"). These radiological impressions were then correlated with the definitive histologic diagnosis available after fine wire localization (FWL) and excisional biopsy. Various potentially contributing patient/surgeon factors were evaluated within category 4 and the conclusions utilized to create a "threshold of treatment" for future patient care and treatment selection.

The diagnostic impressions before FWL and excision biopsy were: 9.2% category 3, 62.4% category 4 and 28.4% category 5 lesions. Among the lesions classified as category 3, all were benign. The positive predictive value of category 4 lesions was 26.5% and for category 5 was 77.4%. Within category 4, those patients under 50 years of age had a malignancy rate of only 5.3%.

The standardized terminology of the BI-RADS lexicon permits an objective quantification of the rate of carcinoma in impalpable breast lesions. Furthermore, by delineating patients with category 4 lesions by age, a reasonable threshold between fine wire excisional biopsies and less invasive procedures (i.e. stereotactic core needle biopsy) can be attained. This results in an increased overall PPV, as well as reduced morbidity, lowered complication rates and a significant cost savings.

MI2

FUNCTIONAL MAGNETIC RESONANCE IMAGING DURING HYPERCAPNEA IN ARTERIOVENOUS MALFORMATIONS

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Baekground: Arteriovascular malformations (AVMs) alter cerebral perfusion pressure, blood flow and vascular reaetivity in both related and unrelated vaseular territories. It is likely that eomplications assoeiated with AVMs and their operative treatment relate to these ehanges in eerebrovascular eireulation The precise manner in whieh AVMs modify eerebrovascular eireulation has not been well eharaeterized. Breath holding during functional magnetie resonanee imaging (fMRI) has been shown to be an effeetive way to study cerebral hemodynamies. No study has reported the application of this teehnique to the understanding of eercbral hemodynamies in patients with AVMs.

Pupose: To asses the effect of AVMs on cerebral hemodynamics

Methods: Ten patients with AVMs will be analyzed by fMRI during a breath holding protoeol. Parametrie analysis of fMRI data to define regions of altered blood flow will be performed. Regions within the vaseular distribution of the AVM will be eompared to other vaseular territories. Further comparison will be made to identical studies performed on the same patients following AVM reseetion and/or embolization.

Results: fMRI with language and motor protoeols is possible in AVM patients. Interim data on 4 patients suggests that AVMs do not ablate the BOLD effect seen in breathhold. There is some evidence for a "steal" phenomenon. Limitations of breathhold in the clinieal population were identified. A superior technique for inducing hypereapnia during fMRI has been developed and optimized.

Conelusion: Alterations in the BOLD effect indueed by hypereapnia may provide important elinical data for patient with pathologies that affeet eerebral perfusion.

MI3

ULTRASOUND BIOMICROSCOPY AS A TOOL FOR MONITORING APOPTOSIS C. Tam*, L. Tan*, G. J. Czarnota, M. C. Kolios, J. W. Hunt, and M. D. Sherar. Department of Medical Biophysics, Princess Margaret Hospital/Ontario Cancer Institute, University Health Network, University of Toronto, Toronto, Ontario, Canada, M5G 2M9.

The use of high-frequency ultrasound biomicroscopy (UBM) as a tool for monitoring apoptosis is a recent discovery. Cellular changes associated with programmed cell death cause areas of tissue undergoing apoptosis to become very bright in conventional ultrasound B-scan images. The long-term goal is to introduce UBM as a non-invasive clinical tool to monitor the response of tumours to chemotherapy and radiation therapy in patients with cancer. In order to demonstrate the applicability of UBM to the clinical setting, we hypothesized that UBM is a) highly sensitive to low levels of apoptosis in heterogeneous mixtures and b) capable of monitoring apoptosis independent of cell type. The effect of apoptotic fraction on ultrasound backscatter was investigated using human acute myeloid leukemia (AML-5) cells cultured in suspension. Mixtures of apoptotic and viable cells in varying proportions were analyzed by ultrasound imaging. Preliminary results failed to demonstrate a correlation between backscatter intensity and apoptotic fraction. In addition, studies were carried out to determine whether the changes in ultrasound backscatter observed in AML-5 cells could be replicated in human melanoma (CRL-1676) cells and human breast cancer (MC7-7) cells. Preliminary results from ultrasound imaging analysis indicate that UBM is capable of detecting apoptosis in these cell lines. Further studies, including histological analyses, will be required to fully characterize the clinical capabilities of UBM.

MI4

Surgical Fluorescence Microscopy

Preliminary Report on Intraoperative Detection of Glioblastoma Multiforme by a Multispectral Fluorescence Guidance System

Victor Yang MASc. Paul Muller MD. Brian WilsonPhD. Peter Herman PhD

Introduction:

Intraoperative identification of tumor can help to define the tumor extent and detect residual tumor tissue, which may increase the effectiveness of both conventional surgical resection and Photodynamic Therapy. In this preliminary report, we present first clinical demonstration of a Multispectral Fluorescence Guidance (MFG) system that performs non-contact fluorescence spectroscopy and microscopy intraoperatively.

Methods:

24 hours before surgery, patient was administered with Photofrin at 2mg/kg of body weight through IV. Intraoperatively, the tissue fluorescence was excited by 405 nm Mercury arc lamp and detected in the visible and near infrared bands (480 - 720 nm). Both spectroscopic and multi-band imaging detection were made simultaneously. Fluorescence measurements were made during, after the surgical resection of tumor tissue, as well as before, during, and after Photodynamic Therapy. Biopsy samples were taken from the tumor perimeters, and examined histologically and photochemically to determine the pathology and concentration of Photofrin uptake.

Results:

Normal and benign brain tissues showed no porphyrin fluorescence, in contrast to tumor tissue which emits characteristic red fluorescence centered at 640 nm. After surgical resection, the MFG system was able to detect residual tumor tissue with sub-millimeter resolution intraoperatively. During Photodynamic Therapy, the MFG system detected photobleaching of Photofrin intraoperatively.

Conclusion:

Surgical fluorescence microscopy is feasible in specially equipped operating room. Our observations suggest that Photofrin used for Photodynamic Therapy may serve as a fluorescence label for malignant gliomas. An intraoperative device such as the MFG system can utilize such label for surgical guidance, which might enhance the completeness of tumor removal and improve survival rate.

Microbiology

MC1

A MODEL OF CHRONIC INFECTION WITH *BURKHOLDERIA CEPACIA* IN CF MICE BY REPEATED INTRANASAL INSTILLATION.

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Background: Presently, most CF patients succumb to chronic *P. aeruginosa* infections However, in recent years, there has been an increase in infections with *B. cepacia*, a novel opprotunistc pathogen *B. cepacia* is now recognized as a cause of infection in immunocompromised hosts and has emerged as a major threat to the CF community, particularly at certain CF centers in Canada, the United Kingdom and the United States In general, infection with *B. cepacia* is similar to that with *P. aeruginosa*: chronic infection interspersed with acute exacerbations and gradual deterioration of lung function However, infection with *B. cepacia* can presage a more malignant course characterized by necrotizing pneumonia, rapid pulmonary deterioration and death Additionally, *B. cepacia* is of great concern because it may be transmitted from person-to-person and is relatively resistant to antibiotic regimens In contrast to the extensive information on the host response *to P aeruginosa*, comparatively little is known about responses to *B. cepacia*

Purpose: To establish a murine model of chronic infection with *B. cepacia* in CF mice to study the response to chronic colonization

Methods: 5 to 8 week old Balb/c, C57BL/6, DBA/2, 129 *Cftr* (-/-) and *Cftr* (+/+) were anesthetized and infected intranasally with 50 L of a PBS suspension of *B. cepacia* (5×10^6 CFU) To achieve chronic infection, 4 instillations were administered over a period of 11 d (every 3rd day). Mice were sacrificed 9 d after last instillation

Results: Using this method we achieved a consistent delivery of *B. cepacia* to the lungs of mice and *B. cepacia* was found to colonize and persist in the lung Both CF mice and controls were able to reduce bacterial load but clearance was more efficient in *Cftr* (+/+) mice *Cftr* (+/+) mice had cleared the infection by 9 d p i whereas significant bacterial burden remained in *Cftr* (-/-) mice At 9 d p.i., we found increased histopathological changes in *Cftr* (-/-) mice that were consistent with CF disease In addition, we found that *Cftr* (-/-) mice recruited a significantly greater amount of neutrophils to the lung as compared to *Cftr* (+/+) ($p<0.02$) Macrophages were also recruited to the lung in similar proportions in *Cftr* (-/-) and *Cftr* (+/+) mice, however levels of surface expression of MHC class II was significantly higher in *Cftr* (+/+) mice ($p<0.01$) which correlated with bacterial clearance

Conclusion: Using a model of repeated intranasal instillation of *B. cepacia* we have achieved a chronic infection in CF mice without the need for immobilizing agents that is consistent with human CF disease

Molecular Biology

MB1

The Role of Wg Protein Localization in Signaling Neighboring Cells

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The protein encoded by Drosophila gene wingless (wg) is an important signaling molecule. It plays a major role in the differentiation and patterning of most embryonic and adult tissues. The Wg glycoprotein binds to receptors on nearby cells. Upon binding unique signaling cascades are induced within those cells. The end result is the induction or repression of specific target genes within the nucleus. Transcripts encoded by the wg gene are tightly localized to apical cytoplasm, which is where the protein is later translated and secreted from. Thus, we hypothesize that localization of wg mRNA and protein within the secreting cells may play an important role in controlling both the direction and strength of the secreted signal. The purpose of the study was to test if subcellular localization of the wg transcript is important for the efficient and directed secretion of the Wg protein. Additionally, we tested whether the levels of protein expression allowed for changes in signaling activity. This was assessed by quantitative Western blots, using anti-tubulin monoclonal antibodies to standardize loadings, and anti-Wg antibodies to determine steady-state levels of Wg expression. In these experiments, the wg open reading frame was placed downstream of a promoter that can be induced in any tissue and at any time in the developing embryo. Downstream of the coding region three different 3' untranslated regions (UTRs) were fused. These different UTRs have been shown to be both necessary and sufficient for localization of the transcripts to different regions of the cell (apically, basolaterally, and uniformly). We found that, when levels of protein expression were equal, protein expressed from mislocalized transcripts was less active. Random localization of transcripts caused a modest drop in signaling activity while basal localization of transcripts caused a near-complete loss of activity. The reasons for loss of protein signaling activity have not yet been determined, nor have the effects on signaling to inappropriate cells.

MB2

New DNA-Based Semliki Forest Virus Vectors For Rapid Protein Production

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The rapid production and purification of high levels of recombinant proteins has important implications both clinically and in a basic research context. The choice of host cell can affect the post-translational modifications of proteins produced Semliki Forest virus (SFV) has emerged as a useful gene expression vector because SFV can infect and over express recombinant proteins in virtually any host cell This is a distinct advantage over the popular baculovirus system, which is limited to insect cells The current SFV system is handicapped by the requirement for *in vitro* manipulation of RNA To overcome this difficulty, we have modified the existing vectors so that the system is wholly DNA-based. Both the replicon vector (encoding SFV polymerase and the protein of interest), and the helper vector, (encoding viral structural proteins), were modified to RNA polymerase II-dependent expression Transfection of the modified replicon plasmid alone generated approximately 20-30 pg of protein per cell, which is comparable to that obtained with the original RNA-based approach, and 10-30-fold more than obtained from a simple expression vector driven by the same promoter or a related plasmid based on the Sindbis virus. Cotransfection of replicon and helper vectors generated viral titers of $10^{\sim}$ infectious particles per ml A single transfection, on one 10cm plate, generated enough virus to produce 0.5 mg of β-galatosidase in the infected target cells. We have further enhanced the system to facilitate rapid cloning and purification of recombinant proteins. The new vector, pSHAME, contains an expanded multiple cloning site, self-cleaving translation enhancer, and two N-terminal epitope tags, FLAG and HIS_{10}, allowing for a two column affinity purification scheme We have used pSHAME in our studies of pRB and pCHX10, two proteins important in retinal development. The system is wholly based in mammalian culture that, unlike bacterial hosts, allows the study of pRB phosphorylation. These new next generation SFV vectors greatly enhance the utility of this expression system and have broad applications in the biological sciences including nucleic acid based vaccination and high output protein production

MB3

CHARACTERIZATION OF THE *Drosophila melanogaster* HOMOLOGUE OF NEDD4 P.C. Henry*, D. Rotin. Cell Biology, Hospital for Sick Children, University of Toronto, Canada, M5G 1X8.

Nedd4 is a ubiquitin-ligase protein which was identified as a binding partner for the proline-rich (PY motif) C-terminus of the β-subunit of the epithelial sodium channel (ENaC) by yeast two-hybrid library screening. A single *Drosophila* homologue of Nedd4 (dNedd4) contains a C2 domain, 3 WW domains (to which the PY motif binds) and a C-terminal Hect domain, a domain with catalytic activity involved in the targeted degradation of other cellular proteins by proteasomal or lysosomal systems. Nedd4 has the potential to participate enzymatically in many cellular pathways via its multiple WW protein-interaction domains. Its biological role and targets in the cell are being studied in *Drosophila*.

dNedd4 cDNA was cloned by screening a *Drosophila* embryo expression library with the PY motif of Inscuteable, a *Drosophila* protein, as bait. Ubiquitous staining of wild-type, whole-mount embryos and larval imaginal discs was observed with RNA *in situ* hybridization. dNedd4 has been localized by chromosome *in situ* hybridization to the left arm of the 3rd chromosome. P-element insertion mutagenesis of the dNedd4 region is currently underway.

The GAL4 driver/UAS promoter system is being used to create transgenic *Drosophila* strains which over-express wild-type and ubiquitin-ligase dominant-negative versions of dNedd4 during different stages of development and in various tissue distribution patterns. A single lethal over-expression pattern of both wild-type and dominant negative forms of dNedd4 was isolated and is now being analyzed.

MB4

ET-1 & Dexamethasone Influence Growth and Differentiation of Fetal Rat Calvarial Cells

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Fetal rat calvarial (RC) cells were isolated from 21 day pregnant white rats. Cells were plated on 35 mm² tissue culture (TC) dishes and grown under appropriate conditions for the duration of all experiments.

RC cells were treated with Endothelin-1 (Et-1) at a concentration of 10^{-8}M and grown for 35 days to assess the effects of Et-1 on RC cell growth. Growth curves were plotted which showed that Et-1 at 10^{-8}M influences RC cell growth in a predictable, reproducible and linear fashion.

RC cells were treated with Et-1 at concentrations ranging from 10^{-11}M to 10^{-6}M for 21 days. From these experiments, it appears that prior to cells forming multiple layers on the TC plates, Et-1 has little to no effect on RC cell growth at all concentrations. After one week as cells form multiple layers, it appears that concentrations of Et-1 (10^{-8}M, 10^{-7}M) increase RC cell growth *vs.* control. After cells have been multi-layered for about one week, low concentrations of Et-1 (10^{-11}M) seem to be inhibitory whereas high concentrations of Et-1 (10^{-7}M) seem to be stimulatory. From these experiments it appears that cell-cell communication may be important in the way that Et-1 influences RC cell growth.

RC cells were treated for 21 days with Et-1, Dex and Et-1 + Dex at 10^{-7}M. These cells were stained and fixed and then compared to control populations. Cells treated with Et-1, Dex and Et-1 + Dex at 10^{-7}M formed more mineralized bone nodules *vs.* control. Cells treated with Dex and Et-1 + Dex formed more nodules than those treated with Et-1 at 10^{-8}M. No significant difference was found between cells treated with Dex and Dex + Et-1. It appears that Dex and Et-1 work in an additive fashion to influence RC cell differentiation which indicates that their signaling pathways work independently of each other.

MB5

MOLECULAR CHARACTERIZATION OF THE *ENTAMOEBA DISPAR* GALACTOSE/*N*-ACETYL-D-GALACTOSAMINE LECTIN

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Amebiasis is a major cause of dysentery in the Third World and contributes to significant morbidity in approximately 50 million people worldwide. Invasion begins with adherence of *Entamoeba histolytica* trophozoites to colonic mucin and intestinal epithelium, a key step mediated by the amebic Gal/GalNAc lectin. Comparison of the lectin from *E. histolytica* (pathogenic in humans) and *Entamoeba dispar* (non-pathogenic in humans) was undertaken in order to elucidate the differential role of this molecule in colonization versus invasion. Surface lectin was less abundant on axenic *E. dispar* when compared to axenic *E. histolytica*, commensurate with differences in lectin (heavy and light subunits) RNA by semi-quantitative RT-PCR. Sequence alignment of homologous lectin genes indicated ~90% conservation at the amino acid level. *In vitro* translation studies showed that both Hgl2 (*E. histolytica*) and Dhgl2 (*E. dispar*) were sufficient for high-affinity binding to multivalent $GalNAc_{19}BSA$. The 1G7 epitope (mapped to residues 482-818) was constitutively present for native lectin on the surface of unfixed, axenically-cultured *E. histolytica* (HM1:IMSS) trophozoites but absent on axenic *E. dispar* (SAW1734cl1AR). However, fixation with methanol/acetone restored the 1G7 epitope on *E. dispar* trophozoites. Furthermore, 1G7 also recognized *E. dispar* lectin (residues 480-900) when transiently transfected into COS7 cells. Anti-sera from patients with amebic liver abscess (ALA) indicated that prior ALA results in a systemic IgG response which recognized *E. dispar* lectin and correlated with clinical cross-protection. *E. dispar* infection alone is capable of eliciting a humoral response specific to *E. dispar* lectin (480-900), suggesting that both shared as well as discrete epitopes are present for homologous lectins. These data, when taken together, provide evidence for gene and conformational regulation of the *E. dispar* Gal/GalNAc lectin which may in part explain the avirulence of this organism when compared to pathogenic *E. histolytica*.

MB6

NEURAL DETERMINATION GENES REVEALED BY EXPRESSION TRAPPING IN EMBRYONIC STEM CELLS. R.M. Seaberg*[1], V. Tropepe[1], W.L. Stanford[2], A. Bernstein[2] and D. van der Kooy[1]. [1]Dept. of Anatomy and Cell Biology, Faculty of Medicine, University of Toronto, Toronto ON M5S 1A8. [2]Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto ON.

Expression trapping is a novel technique in which heterozygous mutations are made in the ES cell genome by the random insertion of a promotorless *lacZ* reporter gene construct which is transcriptionally regulated by the trapped gene. We have developed an assay to test the ability of ES cells to become neural stem cells in serum free media in the presence of leukemia inhibitory factor (LIF). Under these conditions a small proportion (<1%) of single control ES cells proliferate to form floating cell colonies which can passage in culture and differentiate into neurons and glia. Thus, some single ES cells alter their identity to become cells which have the properties that are definitive for neural stem cells: self-renewal and multipotentiality. We have analysed a number of expression trapped ES cell lines for genes involved in neural determination based on two criteria: a dominant genetic effect on the frequency of ES-to-NSC change of fate and a pattern of *lacZ* expression that changes during the ES-to-NSC differentiation. We have identified two transgenic ES cell lines that contain random heterozygous insertions in genes which appear to be important for inhibiting the ES-to-NSC transition. These two cell lines generate ten-fold greater numbers of neurospheres in our assay. Notably, when the neurospheres from these two ES cell lines are passaged they produce similar numbers of secondary neurospheres as control ES lines, indicating that the mutations affect neural determination but not symmetrical division of neural stem cells. Additionally, this assay enables us to identify cell lines containing insertions in genes which may be positive regulators of neural determination, a number of such lines have been identified which generate decreases in neurosphere numbers. Determination of *lacZ* expression has revealed cell lines in which gene expression is high in ES cells, and is downregulated in neurospheres, possibly representing disruption of genes that are important for maintaining the undifferentiated state of the ES cell or for inhibiting the switch to an NSC state. Conversely, we have identified several clones in which the *lacZ* fusion gene is not active in undifferentiated ES cells but is transcriptionally upregulated upon NSC commitment. In addition, two of these cell lines generate reduced numbers of neurospheres than control cell lines suggesting that the endogenous genes regulate ES-to-NSC transition. Supported by MRC Canada.

MB7

LOCALIZATION OF GLOBOTRIAOSYL CERAMIDE VEROTOXIN RECEPTORS IN VARIOUS NEOPLASMS. O. Segal*, A. Nutika, L.E. Becker, R. Stewart, C.A. Lingwood, G.S. Arbus. Departments of Infection, Immunity, Injury and Repair; Pathology; Pediatrics, University of Toronto and Hospital for Sick Children.

Background: Verotoxin (VT) is a cytotoxin produced by enterohemorrhagic E. coli. When it binds to the glycolipid receptor globotriaosyl ceramide (Gb3), VT inhibits protein synthesis as well as inducing apoptosis in target cells. On exposure to VT, the presence of Gb3 on proliferating endothelial cells leads to microangiopathies such as hemolytic uremic syndrome. Gb3 is also expressed on certain tumors, such as astrocytomas and ovarian neoplasms, particularly multidrug-resistant variants. This has led to the investigation of the use of VT as an antineoplastic agent. VT, via its interaction with Gb3, has been shown to induce apoptosis in Burkitt's lymphoma cells and astrocytoma cell lines in vitro, as well as in astrocytoma xenografts in mice.

Objective: To further investigate the potential of VT as a treatment for neoplasms, a broad range of tumors was examined for the presence of Gb3.

Method: Sixteen tumor samples were stained immunohistochemically with VT. These were examined microscopically for the presence of Gb3 on tumor cells or the endothelial cells of tumor blood vessels

Results: There was no staining of tumor cells in any of the samples examined. However, eleven of the sixteen samples showed staining of blood vessels within the tumor, indicating the presence of Gb3 on the endothelial cells. Gb3 positive blood vessels were found in several brain tumors (neuroblastomas, glioblastoma multiforme) as well as bladder tumors, both of low and high grade.

Conclusion: Gb3 is upregulated in the blood vessels of many of the tumors studied By targeting the endothelium produced during angiogenesis in such neoplasms, verotoxin may prove to be a novel therapeutic approach.

MB8

DYNAMIC DISTRIBUTION OF THE APOPTOTIC MACHINERY RESPONSIBLE FOR CHROMOSOMAL DNA DEGRADATION. Joyce So*, Luke Drzymala, Danuta Zvlka, Delphine Lechardeur and Gergely Lukacs. Program in Cell and Lung Biology, The Hospital for Sick Children, University of Toronto, Canada, M5G 1X8.

Apoptosis is the process of programmed cell death involving fragmentation of chromosomal DNA. Apoptosis is mediated by a cascade of proteolytic enzymes called caspases, which leads to the activation of caspase-activated DNase (CAD/DFF40/CPAN). In non-apoptotic cells, CAD forms a heterodimer with its inhibitor (ICAD/DFF45) in a complex called the DNA fragmentation factor (DFF). The dissociation of DFF by caspase-mediated proteolysis of ICAD is required for the activation of CAD in apoptotic cells, and was previously proposed to occur in the cytoplasm. In contrast, immunolocalization of both endogenous ICAD and heterologously expressed DFF indicate that DFF is constitutively expressed in the nucleus of a variety of cells. Using HeLa and MCF7 (caspase-3 deficient) cells in conjunction with indirect immunocytochemistry, we provide evidence showing that staurosporine-induced apoptosis coincides with the cleavage and disappearance of ICAD from the nucleus of HeLa and caspase-3-transfected MCF7 cells but not non-transfected MCF7 cells. This implies that the regulation of CAD activity takes place in the nucleus rather than in the cytoplasm and that caspase-3 is necessary for CAD activation. The expression and activity of caspase-3 increases with staurosporine-induced apoptosis, as monitored by immunoblotting and activity assays. In addition, intracellular caspase-3 translocation is observed upon induction of apoptosis in immunolocalization studies. The apoptotic cascade begins with a complex process of CAD activation by dissociation of ICAD from nuclear DFF. This process requires the presence of caspase-3 and may involve its translocation.

MB9

EFFECTS OF POSTNATAL DEXAMETHASONE AND EXOGENOUS SURFACTANT TREATMENT ON SURFACTANT PROTEIN B MOBILIZATION IN PRETERM RABBITS. Welke TM*, DiGeronimo RJ, and Seidner SR. Pediatrics, University of Texas Health Science Center at San Antonio and Wilford Hall USAF Medical Center, San Antonio, TX.

Surfactant protein B (SP-B) is critical for the endogenous function of surfactant. SP-B mobilization from lamellar bodies to the airspaces of the lungs may facilitate postnatal adaptation. The effects of postnatal dexamethasone (Dex) and exogenous surfactant on postnatal mobilization have not been previously characterized. *Objective*: To measure levels of SP-B and evaluate the effects of postnatal Dex, exogenous surfactant and mechanical ventilation on surfactant mobilization in preterm rabbits. *Design*: Fetal rabbits delivered at 29-days gestation were sequentially randomized to no ventilation (postmortem lavage at birth), spontaneous breathing (± 0.5 mg/kg intravascular Dex, postmortem lavage after 8 and 16 hours), or mechanical ventilation (± Dex, ± 100 mg/kg exogenous Survanta, postmortem lavage after 8 and 16 hours). Spontaneously breathing rabbits were maintained in an isolette with 50% oxygen. Mechanically ventilated rabbits were continuously ventilated with 50% oxygen in individual temperature-controlled plethysmographs adjusting peak inspiratory pressures to regulate tidal volumes. At necropsy, airspaces were lavaged with saline and samples were quantified for SP-B content using a solid-phase, adsorption-based ELISA and for phosphatidylcholine (PC) content via enzymatic colorimetric testing following chemical extraction. *Results*: PC airspace pools were unaltered by Dex, and neither SP-B nor PC content were significantly affected by up to 16 hours of mechanical ventilation. Postnatal Dex significantly elevated SP-B content in airspace lavage at 16 hours of life in both spontaneously breathing ($p < .001$) and mechanically ventilated ($p < .01$) preterm rabbits. Surfactant treated animals following 16 hours of mechanical ventilation had greater than predicted SP-B levels based on the estimated content of SP-B in exogenous surfactant. *Conclusions*: Mechanical ventilation appears to have minimal effects on SP-B, while early postnatal Dex mobilizes SP-B to the airspaces via either increased SP-B secretion or decreased reuptake and/or clearance. Increased recycling of surfactant following instillation of treatment doses may stimulate subsequent SP-B mobilization.

NS1

PROGESTIN RECEPTOR RESPONSES ARE CRITICAL FOR PROGESTERONE'S ANTICONVULSANT EFFECT IN TETANIZED HIPPOCAMPAL SLICES *IN VITRO*.

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PURPOSE: Clinical and laboratory studies suggest that progesterone (P_4) reduces epileptic seizure activity. The mechanisms underlying this effect are not known. The present study determined the effects of P_4 on extracellular evoked responses recorded in the CA1 field of hippocampal slices – both normal and epileptic slices.
METHODS: Brain slices were prepared from ovariectomized rats, with and without estrogen replacement *in vivo*. *In vitro*, slices were made epileptic through repeated tetanization. Slices were then treated with either: P_4 ± RU486 (a P_4 receptor antagonist); allopregnanolone (a P_4 metabolite that potentiates GABA action at $GABA_A$ receptors); RU5020 (a high affinity P_4 receptor agonist) or cholesterol (control).
RESULTS: In non-tetanized slices, allopregnanolone, but not P_4, caused a significant 25 % reduction in the field excitatory postsynaptic potential (fEPSP) and population spike amplitude of evoked responses, as compared to cholesterol controls. In tetanized, epileptic slices, P_4 and RU5020, but not allopregnanolone or cholesterol, caused significant reductions in fEPSPs and population spike amplitudes of evoked responses. P_4 and RU5020 also significantly reduced the duration of tetanic stimulus-induced afterdischarges and the frequency of spontaneous discharges. These effects persisted through the 1 h wash. All responses to P_4 were blocked by pre-treatment of the slice with RU486. Estrogen replacement to ovariectomized rats slightly attenuated P_4's suppression of interictal discharges and evoked responses.
CONCLUSIONS: These data suggest that allopregnanolone, presumably acting via potentiation of $GABA_A$ mediated responses, has more marked anticonvulsive effects than P_4 in non-epileptic hippocampal slices. In epileptic slices, however, P_4 receptor-mediated responses become quantitatively more important as a mechanism for suppressing hippocampal electrical activity.

NS2

PREFRONTAL CORTEX AND EPISODIC MEMORY RETRIEVAL MODE.

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Episodic memory permits one to consciously recollect personally-experienced events as such. Retrieval mode is a major component of episodic memory retrieval; it allows one to adopt and to maintain a mental set of 'thinking back' to a segment of one's subjective past, to treat specified presented stimuli as retrieval cues to particular events in this past, and to experience the product of successful retrieval – should it occur – as a remembered event. The purpose of the present investigation was to utilize the power of multi-study analyses to obtain evidence about specific brain regions subserving the neurocognitive operation(s) comprising episodic retrieval mode. For this purpose, data compiled in our laboratory from four separate PET studies of episodic retrieval memory were analyzed together (n=52). Common regions of brain activation, identified by changes in regional cerebral blood flow by $[^{15}O]H_2O$ PET, were sought in two critical conditions: 1. subjects in a recognition test making 'old'/'new' judgements about previously studied items and 2. subjects in a recognition test making 'old'/'new' judgements about previously non-studied items. This approach allowed the localization of brain activations independent of retrieval success. PET data were processed using the statistical parametric mapping technique. The multi-study analysis of PET data identified three right prefrontal and two left prefrontal cortical sites, as well as a region in the anterior cingulate gyrus where neuronal activity is higher during attempted retrieval of episodic information than it is during appropriate control tasks, regardless of the outcome of the attempt. The right prefrontal sites were near the frontal pole (BA 10), frontal operculum (BA 47/45), and lateral dorsal area (BA 6/8/9). The two left prefrontal sites were homotopical with the right frontal pole and opercular sites. Many previous functional neuroimaging studies of episodic memory retrieval have reported activations near the frontal retrieval mode sites identified here, although their function has not been clear. We argue that many of these have served the function of retrieval mode, and propose that retrieval mode activations largely if not entirely account for the frontal hemispheric asymmetry of retrieval as previously described by the HERA model (Tulving et al., Proc. Natl. Acad. Sci. USA, 1994).
O.G. was supported by a summer scholarship from MRC Canada.

NS3

SUBSTANTIA NIGRA PARS COMPACTA NEURONS THAT DEMONSTRATE REGENERATIVE CAPACITY *IN VIVO* DO NOT EXPRESS A DOPAMINERGIC PHENOTYPE.

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Parkinson's disease is a neurodegenerative condition that is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNC) and the development of tremor, rigidity and bradykinesia. It has been previously demonstrated that neurons in the SNC, presumably dopaminergic, will extend axons through peripheral nerve grafts that are implanted into either the striatum or the medial forebrain bundle. Refinement of this technique could possibly provide a means to increase survival of SNC neurons and establish collateral innervation of dopamine-deficient regions in the striatum. In the present study, we implanted autologous tibial nerve grafts into either the striatum or the medial forebrain bundle. Fluorogold was used to retrogradely label the soma of neurons that had extended axons through the grafts, and demonstrated that the labeled cells were large-diameter neurons, predominantly confined to the SNC. Although the morphology and location of the fluorogold-positive cells were indicative of a dopaminergic phenotype (>85% of neurons in the SNC produce dopamine), double-labeling immunofluorescence with fluorogold and tyrosine hydroxylase (a key enzyme in dopamine production) showed that most fluorogold-positive cells did not express tyrosine hydroxylase. These results suggest that SNC neurons that are stimulated to extend axons through peripheral nerve grafts undergo an alteration in phenotype and suppression of dopamine expression.

NS4

THE EFFECT OF NEURITE TRANSECTION AND EXTRA-CELLULAR CALCIUM ON RAT SYMPATHETIC GANGLION CELL DEATH IN VITRO

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Calcium entry into neurons secondary to excitotoxic insults is believed to trigger neurotoxic events leading to neuronal death. However, the role of calcium influx in neuronal death after neurite transection that is independent of excitotoxicity has not been clearly defined. This study assesses the effect of varying extra-cellular calcium concentration ([Ca2+]e) from 50nM to 5mM on cell death, in 14 day old cultures of dissociated sympathetic neurons from the superior cervical ganglia of newborn rats. The neurites were transected with a custom made injury device and cell death was assessed with propidium iodide and fluorescence microscopy. The results are as follows: first, neurite transection was found to cause a significant increase ($p<0.05$) in cell death at all [Ca2+]e studied, but there was no significant difference in mortality at the various [Ca2+]e, second, cell death significantly increased between 2hrs and 24hrs post-injury at all three [Ca2+]e, and third, cell death decreased with increasing distance between the cell body and the transection site, exhibiting a significant decrease in mortality at distances greater than 0.66mm, irrespective of [Ca2+]e. These results suggest that influx of extra-cellular calcium is not responsible for post-transection cell death, implying that calcium release from internal stores or calcium independent cell death mechanisms are triggered by neurite transection.

OB1

COMPARISON BETWEEN THE USE OF LOW-DOSE MICRONIZED PROGESTERONE AND MEDROXYPROGESTERONE ACETATE IN HORMONE REPLACEMENT THERAPY. S. Lee*, S. Wong, W. Wolfman. Department of Obstetrics & Gynecology, Toronto General Hospital, University Health Network, Faculty of Medicine, University of Toronto, Canada, M5G 2C4.

Background: The main purpose of using progesterone in hormone replacement therapy (HRT) is to reduce the frequency of endometrial hyperplasia amongst postmenopausal women. The poor absorption and rapid clearance of progesterone led to the development and use of progestin as a synthetic substitute. The evolution of a micronized form of progesterone improved upon the issue of gut absorption and side effect profile. This raised the question of using this new form of natural progesterone in established HRT regimens such as in continuous daily combination with estrogen. **Objectives:** The aim of this study was to compare the use of daily estrogen with either micronized progesterone 100 mg or medroxyprogesterone acetate (MPA) 2.5 mg. The effects of these combinations on uterine bleeding, endometrial changes and breast parenchyma were investigated. **Study Design:** A retrospective chart review utilized the following inclusion criteria: 1) patients aged 40 years or older; 2) postmenopausal as defined by the absence of menses for a minimum of 6 months with symptoms of estrogen deficiency (e.g. hot flushes), FSH and estradiol levels indicative of a menopausal state or patients having undergone hysterectomy. Data sources included patient self-report, endometrial biopsy and mammographic results. Pearson's chi-square tests were applied to determine statistical significance. **Results:** Preliminary results have identified 506 postmenopausal patients, with an estimated total of approximately 650 patients upon study completion. At present, 112 patients take estrogen with continuous micronized progesterone 100 mg (average duration: 11.5 months) and 46 take estrogen with continuous MPA 2.5 mg (average duration: 2.2 years). There were no significant differences found between the two combinations with respect to side effects, bleeding pattern, endometrial biopsy or mammography. **Conclusion:** The use of estrogen in combination with continuous low-dose micronized progesterone (100 mg) produces minimal side effects and is a safe alternative to continuous estrogen and medroxyprogesterone acetate (2.5 mg) for a one year duration.

OB2

IMPROVED COLPOSCOPIC MANAGEMENT OF WOMEN DIAGNOSED WITH ABNORMAL CERVICAL CYTOLOGY DURING PREGNANCY. A.Tandon,B.Sc*,J.McCoshen,Ph.D, F.Guijon,M.D. Department of Obstetrics and Gynecology and Reproductive Sciences, Faculty of Medicine, University of Manitoba.

This study evaluated the accuracy of colposcopy and colposcopically directed biopsies in pregnant women with abnormal cervical cytology. Five hundred and ninety-one pregnant patients were referred to the colposcopy clinic between 1984 and 1998 for evaluation of abnormal Pap tests. One hundred and sixty-six of these women underwent colposcopically directed biopsies in the antepartum period and all treatments were performed in the postpartum period. When compared to the histologic diagnosis in these patients, the colposcopic findings are in significant agreement (Kappa=0.729; P=0.001). Success rates of the various treatments performed were all above 90.0%. Three patients exhibited histologic evidence of recurrence of lesion one year after treatment.

We conclude that colposcopic assessment is important in the antenatal period and poses not risk to pregnancy. Also, treatment of cervical intraepithelial neoplasia (CIN) in pregnancy can be postponed until postpartum and after re-evaluation.

OB3

DYSFUNCTIONAL UTERINE BLEEDING IN WOMEN WITH CHRONIC RENAL FAILURE. **K.A. Wilson*, J. Zaltzman, M. Goldstein, and C. Derzko. Department of Nephrology and Department of Obstetrics & Gynecology, St. Michael's Hospital, University of Toronto, Canada, M5C 2T2.**

A significant number of women with chronic renal failure (CRF) experience menstrual disturbances ranging from amenorrhea to polymenorrhea or menorrhagia. Menstrual dysfunction leads to considerable morbidity and personal distress for women. Relatively little information exists about the menstrual patterns of women with CRF, and the pathophysiological basis of this menstrual dysfunction remains poorly understood. *The objectives of this study were: 1) to determine the prevalence of menstrual dysfunction among women with CRF; 2) to characterize the menstrual patterns of women at all stages of CRF and its treatment; 3) to correlate altered menstrual patterns with treatment modality, endocrine profile, renal function tests, hematology, and medication use, in an attempt to identify factors associated with altered menstrual patterns among women with CRF.* A case series of 72 women aged 20-50 with CRF participated in the study, including 4 with untreated progressive renal failure, 24 being treated with dialysis, and 44 post renal transplantation. Each participant underwent a structured interviewed and gave a blood sample to measure LH, FSH, prolactin, estradiol, urea, creatinine, and hemoglobin. Basic demographic information, treatment modality, and medications were also recorded. Preliminary analyses suggest that the overall prevalence of menstrual dysfunction among women with CRF is high, at 79%. Women with progressive renal failure commonly report disruption to their menstrual cycles including oligomenorrhea and amenorrhea. These hypomenorrheic patterns are also common among women being treated with dialysis. Transplantation appears to lead to resumption of regular menses, but menorrhagia is common in this group. Further analyses are currently underway to clarify these issues, and to identify factors associated with menstrual dysfunction in this population. A better understanding of the causes of menstrual dysfunction in women with CRF may facilitate the development of interventional strategies to positively influence the health and quality of life of these patients.

ON1

THE HYALURONAN RECEPTOR RHAMM REGULATES PROGRESSION AND INVASION OF PROSTATE CANCER M.C.Y. Chang*, D. Bagli. Division of Urology, The Hospital for Sick Children, University of Toronto, Toronto, Canada, M5G 1X8

Lack of proven therapy makes metastatic disease largely responsible for mortality in prostate cancer (CaP). Metastasis requires a complex integration of cell motility and matrix degradation. Although the mechanisms of motility are not completely understood, there is clearly an interaction between extracellular matrix (ECM) macromolecules and their cell surface receptors. One ECM receptor, RHAMM, binds hyaluronan (HA), mediates motility in many cell types, and has recently been linked to the progression of breast cancer. We hypothesize that functional expression of RHAMM mediates progression to metastatic CaP. Immunohistological studies of human CaP tumors obtained from radical prostatectomy show stronger RHAMM staining in tumor than normal cells and correlate with Gleason grade. In addition, immunolocalization of RHAMM shows weaker cytoplasmic staining in the Dunning rat CaP cell line AT-1 (low—) than in the MatLyLu line (high—motility/metastatic potential), which was derived from AT-1 by serial passages *in vivo*. Western analysis indicates that RHAMM expression is progressively enhanced in a Noble rat CaP system of *in vitro* progression (NbE, noninvasive<NbMC2, low motility/invasivity<<NbF, high motility/invasivity). Moreover, blocking HA-RHAMM interactions with peptides or antibodies significantly reduces random motility of MatLyLu cells to levels similar to AT-1 parental cells. Since RHAMM is emerging as a prototypical example of a "transitional" molecule whose activity increases during the initiation of a diseased (i.e. metastatic) state, these results suggest RHAMM may be an ideal target to selectively inhibit metastatic progression of CaP.

ON2

EFFECTS OF ALLOGENEIC BONE MARROW TRANSPLANTATION ON BONE MINERAL DENSITY IN WOMEN D. Hui*, C. Derzko, H. Messner. Department of Obstetrics and Gynecology, St. Michael's Hospital, Department of Hematologic Oncology, Princess Margaret Hospital, University Health Network, University of Toronto, Canada, M5G 2M9

Background: Bone marrow transplantation (BMT) has become a highly successful mode of treatment for many disorders of bone marrow, reducing the mortality associated with these diseases. However the longterm effects on morbidity have not been fully characterized. Osteoporosis represents a disease which recipients of BMT may be at increased risk of developing. Monitoring long term effects of BMT on bone mineral density is important in the elucidation of the consequences of BMT on overall bone composition and architecture.

Objectives: To investigate the long term effects of BMT on bone mineral density.

Methods: Retrospective analysis of 66 female BMT recipients at Princess Margaret Hospital between 1980 and 1998. Diagnosis, corticosteroid and cyclosporin A use patterns, use of hormone replacement therapy, seventy of graft-versus-host disease, and serial bone density measurements were analyzed.

Results: Bone marrow transplantation effects a reduction in bone mineral density, thus increasing the risk of osteoporosis-associated morbidity in this population of women. The degree of increased risk may be modified by numerous interventions.

ON3

Proliferation Factors in Human Cervix Carcinoma and Their Possible Clinical Significance Stephen C. Juvet B.Sc. and Richard W. Tsang M.D., FRCP(C). One of the features of cancer is unrestrained tumour growth. Hence, tumour cell proliferation is an important parameter of tumour biology. In human cervix carcinoma, traditional prognostic factors have included tumour size, clinical stage, hemoglobin level, and overall radiotherapy treatment time (OTT). The negative prognostic effect of a long OTT suggests that rapid tumour proliferation is responsible for treatment failure. We hypothesized that proliferation rate, as reflected by bromodeoxyuridine (BrdU) uptake would be prognostic in cervix cancer. In addition, we hypothesized that expression of endogenous proliferation-associated proteins (proliferating cell nuclear antigen [PCNA] and Ki-67) and the mitotic index (MI) would be correlated with BrdU incorporation and would also be predictive of disease-free survival (DFS). Patients were given an IV dose of BrdU approximately 8 hours prior to biopsy during examination under anaesthesia (EUA). One portion of each biopsy was sectioned and adjacent sections were stained immunohistochemically with anti-BrdU, anti-PCNA and MIB-1 (anti-Ki-67) antibodies. The number of tumour cells stained positively in 10 fields at 400x (approx. 1000 cells total) were expressed as the labelling index (LI), the percentage of the total number of tumour cells counted. The remainder of each biopsy was evaluated flow cytometrically for the BrdU LI and potential doubling time (Tpot). A total of 114 patients were followed prospectively to determine DFS and clinical parameters. The results demonstrate that the clinical factors, particularly tumour size and initial hemoglobin level, were most predictive of DFS ($p = 0.0017$ and 0.0013, respectively). The MIB-1 LI and PCNA LI correlated strongly with histological grade ($p = 0.0189$ and 0.0092, respectively), indicating that there is a strong relationship between histological grade and growth fraction. There was a tendency for increasing BrdU LI, assessed by flow cytometry and histologically, as well as MI to predict for poorer DFS, although these results were not statistically significant. Neither the PCNA nor the MIB-1 labelling indices were predictive. However, for small tumours (≤5.5cm), there was a stronger relationship between the BrdU LI and DFS, with borderline statistical significance ($p = 0.0695$). In conclusion, tumour cell proliferation (as measured by BrdU LI) rather than tumour growth fraction (PCNA LI and MIB-1 LI) is associated with poorer DFS in human cervical cancer, but these parameters were not predictive when tumour size and hemoglobin level were taken into account.

Ophthalmology

OP1

VISUAL PROGNOSIS FOLLOWING OPEN GLOBE TRAUMA. D. Yuen*, R. Johnston. Department of Ophthalmology, Saint Michael's Hospital, Faculty of Medicine, University of Toronto, M5B 1W8.

The purpose of this study was to identify clinical factors on initial presentation that predict final visual outcome following open globe trauma. To this end, the charts of 40 patients presenting with open globe trauma at St. Michael's Hospital between 1985 and 1998 were retrospectively reviewed. Clinical factors at initial presentation, post-trauma complications, and final visual acuity data were collected and analyzed. Of the 40 cases studied, 37 (92%) were male. The average age was 41 years (range: 17 to 82 yrs). Among the 23 patients (58%) who presented with an initial visual acuity (VA) of hand motions vision or worse, two patients (9%) had 20/40 vision or better after at least 6 months of follow-up. Of the 10 patients (25%) who presented with an initial VA of counting fingers or better, 4 patients (40%) had 20/40 vision or better after 6 months. Five out of the 6 eyes which presented initially with no light perception were enucleated. 11 eyes (28%) underwent enucleation. No patients developed sympathetic ophthalmia, two eyes (5%) developed endophthalmitis, and 12 eyes (30%) developed a retinal detachment. Statistical analyses found that initial Snellen visual acuity, location of injury, and the presence of a fixed pupil or a relative afferent pupillary defect were significantly related to final visual acuity ($p<0.005$, Chi-square test). Interestingly, no significant correlation could be shown between type of injury (as defined by the Ocular Trauma Classification Group system) or pars plana vitrectomy and final visual acuity. Future work will analyze the relationships between the previously mentioned clinical factors and vision-specific quality of life ratings. The results of this study thus indicate that initial visual acuity, the location of injury, and the presence of a fixed pupil or relative afferent pupillary defect are all significant predictive factors for final visual outcome. The identification of such prognostic factors may aid clinicians in more accurately predicting final outcome, and in selecting the optimum management for the open globe trauma patient.

Otolaryngology

OT1

DISCRIMINATION OF FREQUENCY AND HARMONICITY OF MAJOR TRIADS IN NORMAL LISTENERS AND COCHLEAR IMPLANTEES.
E.J. Propst*, B.C. Papsin MD FRCSC, K.A. Gordon MA, J. Figueiredo and R.V. Harrison PhD, DSc. The Cochlear Implant Program, The Hospital for Sick Children, University of Toronto, Canada, M5G 1X8.

Background: Cochlear Implants electrically stimulate auditory nerve fibres in the cochlea via a coil containing electrodes when hair cells of the organ of Corti have degenerated or fail to develop. Since there can only be a maximum of 24 electrodes in a Nucleus Cochlear Implant, ranges of frequencies are assigned to individual electrodes.
Introduction: This experiment determined the ability of cochlear implant users to discriminate pure-tone frequencies in isolation and in the musical context of a major triad (C major chord).
Method: Ten normally-hearing volunteers and 6 cochlear implantees were studied using a three-interval forced-choice paradigm. Listeners were asked to discriminate between the probe pure tones (560, 2041, 5754 Hz which corresponded to frequencies in electrodes 18, 11 and 4 in the cochlear implantees MAPped in BP+1) and a variable pure tone which varied in frequency within trials. Psychometric functions were generated and the frequency at which a listener could tell the tones apart (df) was determined. Next, a C major triad (C=523.25, E=659.26, G=785.99) was presented and the third was varied in frequency until the listener could detect a difference. All tones were presented for 300ms and the chord complex was presented for 800ms via loudspeaker in a single-walled semi-reverberant IAC sound booth at 75 dBA with a 50 ms rise/fall time.
Results: Mean dfs increased with increasing frequency of the probe tone in both normal listeners and cochlear implantees. Mean dfs were significantly higher (t-test) for the cochlear implantees for the 2041 and 5754 Hz probe tones but not for the 560 Hz probe tone. For the major chord the df was significantly higher in the implanted listeners. All six implanted individuals were able to discriminate two tones within an electrode at low frequencies, four were able to do this at the mid and high frequency probe frequencies. All six implantees were able to discriminate within an electrode within the context of a musical chord.
Conclusion: Cochlear implantees are able to perform frequency discrimination and harmonic discrimination beyond the theoretical capabilities of their implants. Clearly cues must be available as a result of signal processing to allow this to happen.

Pediatrics

PE1

PEDIATRIC TYPE 1 DIABETES HYPOGLYCEMIA MANAGEMENT – IS THERE A CORRELATION BETWEEN ADHERENCE TO RECOMMENDATIONS AND HbA_{1c}? N. Crispino*, D. Wherrett. Division of Endocrinology, Department of Pediatrics, Faculty of Medicine, University of Toronto, Canada, M5G 1X8.

Proper management of hypoglycemia is essential to the prevention of the complications of type 1 diabetes. The objective of the study is to determine i) how children and teens with type 1 diabetes who attend the diabetes clinic at the Hospital for Sick Children manage hypoglycemia, ii) the frequency of adherence to recommendations for management in these patients, iii) whether adherence to recommendations is associated with lower HbA_{1c} values, and iv) the incidence of hypoglycemia in this population.

A questionnaire addressing incidence of hypoglycemia and management behaviours was completed by 169 children/teens with type 1 diabetes and/or their parents. Hypoglycemia management knowledge and practice were assessed by converting relevant responses to a Knowledge or Practice Score, totaling three and eight, respectively. Hypoglycemia incidence, management behaviours, and frequency of adherence to management recommendations were determined using descriptive statistics. The association between self-reported adherence to hypoglycemia management recommendations and year mean HbA_{1c} was evaluated using simple correlation and multiple regression.

Seventy-five percent of respondents normally carry identification, but only 61% were carrying identification at the clinic visit. Thirty-six percent of individuals were not carrying any form of fast-acting glucose. 30% were not carrying any form of treatment at all. One or more episodes per week of mild or moderate hypoglycemia was reported by 58.9% of participants. Thirty-seven percent of respondents consistently overtreat hypoglycemia. The mean score on the hypoglycemia management Knowledge Score was 2.2±0.8 (± SD). The mean score on the hypoglycemia management Practice Score was 5.1±1.8. The results of the analysis of the association between adherence to hypoglycemia management recommendations and HbA_{1c} are pending.

Based on the Knowledge Score, participants have fair to good knowledge of the recommendations for treatment of hypoglycemia. However, it has been demonstrated that this knowledge is not applied consistently, as evidenced by the percentage of individuals who actually wear identification, the tendency to overtreat hypoglycemia, and the moderately low mean Practice Score.

PE2

CLINICAL RELEVANCE OF FUNCTIONAL MEASURES IN CHILDREN WITH JUVENILE ARTHRITIS AND OTHER MUSCULOSKELETAL DISABILITY
Helen Dempster*, Michelle Porepa, Nancy Young, Brian Feldman. Department of Pediatrics, Hospital for Sick Children, Toronto, Ontario, M5G 1X8.

The Childhood Health Assessment Questionnaire (CHAQ) is a self or parent report questionnaire measuring disability in children with arthritis. Despite its widespread use, the clinical significance of the CHAQ score is not well understood.
Objective. To determine cut off levels of the CHAQ that correspond to mild, moderate and severe disability, and to determine the minimal clinically important difference in CHAQ scores. ***Methods.*** Parents of children with inflammatory arthritis were consecutively sampled from the rheumatology clinics at the Hospital for Sick Children and at the Bloorview MacMillan Centre. They completed 3 questionnaires administered by a trained interviewer at a single visit. 1. The CHAQ. 2. A categorical disability scale. 3. A categorical change scale. Finally, parents were asked to redo the CHAQ after considering hypothetical situations in which their child's disability was reduced or increased "by just enough to make a difference." ***Results.*** 131 families were recruited. Index children had a mean age of 9.6 years (1-18 yr.), 69% were female, and the median Steinbrocker disability score was 1 (range 1-4, IntQ Range of 1). The mean current CHAQ score was 0.36 (median 0.125, range 0-2.5) where 0=no disability and 3=most severe disability. There were 45 children with no disability, 47 with mild disability, 32 with mild to moderate disability, and 7 with moderate disability. The median CHAQ score for each disability category was as follows: no disability: 0 (IntQ Range of 0), mild disability: 0.125 (IntQ Range of 0.41), mild to moderate disability: 0.625 (IntQ Range of 0.875), and moderate disability: 1.75 (IntQ Range of 0.59). The difference between these values was statistically significant ($p \leq 0.0001$). Results from the hypothetical scenarios indicated that a clinically significant improvement was represented by a median change of 0.125 in CHAQ scores whereas a clinically significant deterioration was represented by a median change of 0.75 in CHAQ scores. ***Conclusion.*** We have determined the clinical meaning of the CHAQ scores and the minimal difference that is meaningful to patients. These results will allow us to plan more relevant clinical trials and develop a better understanding of our patients' disabilities.

PE3

PSYCHOSOCIAL IMPACT OF CHRONIC ILLNESS IN CHILDHOOD L Puchalski Kitchie*, R J Hilliard Hospital for Sick Children, University of Toronto

BACKGROUND Chronic illness is common in childhood, with estimates ranging from 5-31%. While most children adjust well to the stress of chronic illness, there is an increased incidence of psychosocial maladjustment in this population, with both long and short-term implications for the child's wellbeing. As much of the research to date has investigated these issues within specific diagnostic groups, little information is available regarding commonalties across categories of chronic illness. Little is known about the degree to which clinicians recognize and address psychosocial difficulties in their patients with a chronic illness. OBJECTIVE To assess the psychosocial impact of chronic illness in childhood and variables related to the severity of impact, and to determine from the parent's perspective if and how physicians should address these psychosocial issues. METHODS A semi-structured qualitative interview was conducted with parents of 9 chronically ill school aged children attending a variety of outpatient clinics at the hospital for sick children. The qualitative interview included diagnosis and age of onset, limitations imposed by the chronic illness, impact of the chronic illness, impact on the family, awareness and use of support services, and parents' opinion of the physician's role. Parents were encouraged to discuss additional areas of interest or concern. Parents completed the Child Behavior Checklist (CBC)-a quantitative measure of psychosocial adjustment. Parents and physicians completed a 3-item visual analogue scale to assess illness severity, expected course, and anticipated future psychosocial impact. RESULTS Incidence of psychosocial maladjustment was found to vary with the measure used. While the CBC identified only 2 children as having difficulties, analysis of the endorsed items suggests caution in the interpretation of the CBC in this context. Based on the interview data, psychosocial difficulties were common among this group of chronically ill children, regardless of diagnosis, with disability and disruption of normal childhood activities emerging as important variables in determining the severity of the psychosocial impact. No trend was evident on comparison of parent and physician visual analogue ratings. CONCLUSIONS It is recommended that physicians caring for chronically ill children should periodically and specifically inquire into psychosocial functioning.

Psychiatry

PS1

THE CONSTRUCT OF AFFECTIVE LABILITY **S.R. Wiesenthal*, P. Links. Arthur Sommer Rotenberg, Chair of Suicide Studies, St. Michael's Hospital, University of Toronto, Canada.**

Affective Lability (AL), an unsettling feature of several psychiatric disorders, is characterized by frequent, and short-lasting mood-swings within a 24-hour period. Previously, AL was implicated as a risk factor for attempted suicide. The Visual Analogue Mood Scale (VAMS), a known self-report measure of general mood, and mood variability, is the most direct method of measuring AL, however, since it requires repeat measures, there is a high non-compliance rate. Recent studies failed to demonstrate a relationship between the VAMS and a quicker technique for measuring AL, the Affective Lability Scale (ALS). This suggests that AL is not a form of affective disorder or biphasic mood swings, and thus is not related to concepts measured by the ALS. The purpose of our study was to examine the construct of AL in association with impulsivity, reward dependence and neurotic traits which are thought to be associated with AL. Approval to approach patients was sought from their physicians and nurses. Patients were asked for signed consent after full explanation of procedures. Participants completed the Anger, Irritability, and Assault Questionnaire, a measure of impulsivity, the Diagnostic Assessment of Personality Pathology, a measure of neurotic traits, and the Temperament and Character Inventory, a measure of reward dependency. Since this study was an amendment to a previous study, the participants completed the ALS, the General Behavior Inventory, the Suicidal Behavior Questionnaire and the Symptom Checklist 90 which were used in the previous study. Following this, the subject was required to fill out the VAMS twice daily for two weeks. 32 inpatients were approached, 50% signed consent forms, while 50% refused. 38% completed all forms, 63% only partially completed the study. The diagnoses of the people who completed the study include Major depression, Substance abuse and Borderline personality disorder, psychotic but not schizophrenic), and Bipolar illness. The correlations are still pending completion. The VAMS auto-correlation scores will be compared with scores from the other measures. This study is relevant in that impulsivity, reward-dependence and neurotic traits may be predictors of suicide risk. Identification of these behaviors in individuals would play an invaluable role in identifying individuals at risk, thus aiding in the prevention of suicide.

Respirology

RE1

SLEEP TIME AND STRUCTURE IN PATIENTS WITH REFRACTORY HYPERTENSION AND OBSTRUCTIVE SLEEP APNEA A. Lazarescu*, A.G. Logan, R. Tkacova, R.S. Leung, F. Fitzgerald and T.D. Bradley. Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Studies in normal human subjects have shown that just a single night of sleep deprivation can cause elevations in systemic blood pressure during the following day. Such studies therefore suggest the potential for sleep deprivation to contribute to the development of hypertension in some individuals. Obstructive sleep apnea (OSA) is a disorder in which sleep is disrupted by frequent arousals and the total amount of sleep can be reduced. Patients with OSA often have hypertension, but factors that distinguish those patients who have hypertension from those who do not have not been elucidated. One possibility is that the relative degree of sleep disruption or deprivation might be involved in the pathogenesis of hypertension in these patients. We hypothesized that OSA patients with refractory hypertension have a reduced amount of sleep and lower sleep efficiency than OSA patients without hypertension. We analyzed sleep studies of 31 refractory hypertensive patients with OSA and 36 normotensive patients with OSA, matched for age, sex, body mass index and apnea-hypopnea index (AHI). OSA patients with and without refractory hypertension had similar degrees of OSA (AHI 29.5±3.4 vs 32.1±3.3/hr sleep, p=0.59, lowest S_aO_2 83.1±1.2 vs 79.2±1.8%, p=0.08) and of sleep fragmentation (arousals 34.3±4.1 vs 33.7±3.6/hr sleep, p=0.91). However, refractory hypertensive patients with OSA had significantly lower total time asleep (277.5±16.7 vs 321.8±11.4 minutes, p<0.03), lower sleep efficiency (69.1±3.4 vs 81.3±2.4%, p<0.005), longer sleep latency (26.9±5.0 vs 16.2±2.3 minutes, p<0.05), and a higher percentage of sleep period time spent awake (26.3±3.3 vs 14.7±2.1%, p<0.003) than normotensive patients with OSA. There was also a significantly lower percentage of time spent in REM sleep (11.3±1.3 vs 14.8±1.2%, p<0.05) in the refractory hypertensive patients. Refractory hypertensive patients with OSA sleep less, have less REM sleep, take longer to fall asleep and are awake for longer periods of time than normotensive patients with OSA. Our findings indicate that refractory hypertension in patients with OSA is associated with a state of relative sleep deprivation.

SU1

Assessing Self-Esteem in Children with Facial Paralysis: A Review of Available Tools

Martin Jugenburg, B.Sc., Pam Hubley, R.N., M.Sc., NP, Holly Yandell, R.N., M.Sc., NP, Dr. R.M. Manktelow, Dr. Ronald M. Zuker, Dept. of Plastic and Reconstructive Surgery, The Hospital for Sick Children and The University Health Network, Toronto, Ontario, M5G1X8

Research in surgery has traditionally focused on quantitative issues, while ignoring the qualitative aspects of its impact on patients. The purpose of this research project was to identify appropriate tools to address a gap in the psychosocial assessment of surgical patients, to allow for the assessment of the impact of corrective surgery on children with facial paralysis. The outcome of this investigation is a recommendation for an adoption of Harter-based assessment tools for research purposes, and the Rosenberg Measure of Self-Esteem for clinical use. These tools will then allow health-care professionals to assess the psychosocial impact of structural deformities on the patient, and to predict the effect of the corrective surgery on self-esteem.

SU2

BIOMECHANICAL EVALUATION OF METHODS OF FIXATION FOR REVERSE OBLIQUITY INTERTROCHANTERIC FEMORAL FRACTURES. J. Lobo, P. Kuzyk*, D. Whelan, S. Aksenov, E. Schemitsch. Department of Orthopedics, St. Micheal's Hospital, University of Toronto, Canada.

Reverse obliquity intertrochanteric femoral fractures (ROIFF) are difficult to treat because of implant failure and medial displacement of the distal femur. The Dynamic Hip Screw (DHS), Dynamic Condylar Screw (DCS) and Intramedullary Hip Screw (IMHS) may be used for fixation, but data does not exist to suggest an optimal implant for this specific fracture. **Methods:** Twelve matched pairs of human femora were equally distributed among 3 groups (DHS [n=4], DCS [n=4], and IMHS fixation [n=4]) according to their Singh index. ROIFF were created in the left femora at a 33° angle. Femora were placed in methylmethacrylate molds at their distal ends to a length of 24cm. Stiffness, strain, and lateral displacement of the proximal femur were determined in four positions (25° adduction, 25° abduction, 25° and 90° flexion) with cortical contact across the fracture site. A 1cm gap was created at the fracture site, tests were repeated in all positions, and femora underwent failure testing in 25° adduction. Data was normalized to the intact contralateral femur to eliminate variability between samples. **Results:** There was no difference in stiffness between implants after osteotomy (DHS 67.0±7.9%, DCS 76.1±10.6%, IMHS 52.5±11.9% of control stiffness [p=0.32]). However, after gap creation, stiffness of all implants was reduced (p=0.03) and there was a significant difference between implants (DHS 46.6±3%, DCS 22.9±2%, IMHS 53.7±7.8% of control [p<0.05]). There was no significant difference in lateral displacement of the proximal femur between implants before (p=0.92) or after (p=0.26) gap creation. Similar results were noted for abduction and flexion. Yield points were significantly different (DHS 3409±173N, DCS 2566±173N, IMHS 4644±518N [p=0.03]). The DHS and DCS implants failed in varus through the greater trochanter while the IMHS shortened through the proximal femur. **Discussion:** Our results suggest that the choice of implant is not biomechanically important when cortical contact can be achieved. In cases of significant bone loss the IMHS may provide greater stability and higher resistance to deformation than the DCS or DHS implants.

SU3

INTER-RATER AND INTRA-RATER RELIABILITY IN WOUND SIZE ASSESSMENT. C.D. McDermott*, J. Mahoney, L. Teague. Division of Plastic Surgery, St. Michael's Hospital, University of Toronto, Canada. M5B 1W8.

BACKGROUND: Wound measurement must be done using an accurate and consistent method that is efficient in determining the level of wound healing in the clinic setting. It is the aim of this study to determine the inter-rater (performed by more than one investigator) reliability by comparing wound length and width measurements, as well as wound tracings performed by three trained investigators (wound care specialist, medical student, and registered nurse (RN)). This study was also used to investigate the intra-rater (performed by one investigator) reliability of various wound area measurements obtained from linear measurements and wound tracings.

METHODS: Wounds of all types, with well-defined borders, were included in this study (n=31). Each investigator measured wound length and width, used to calculate wound size with respect to the area of a rectangle and ellipse; and traced the perimeter of the wound onto a grid, whereby wound area was determined in terms of rectangle and ellipse areas, counting grid squares, and computer analysis of wound size.

RESULTS: Linear measurements taken directly from the wound site showed no significant differences between the three investigators. In contrast, there were significant differences in measurements taken from wound tracings between the specialist and those taken by either the student or RN. There was also a significant difference between the area calculated from wound tracings using computer analysis with those values calculated by other methods.

CONCLUSIONS: We conclude that linear measurements of wounds demonstrate significant inter-rater reliability, whereas measurements taken from tracings show a lack of inter-rater reliability, indicating a need for greater education in wound tracing technique and objective evaluation of wound dimensions by health care providers. This study has also shown a lack of intra-rater reliability when comparing wound area measurements calculated from computer analysis of tracings to those obtained from other methods; these other methods do, however, provide suitable baseline measurements for evaluation of wound healing.

SU4

BIOMECHANICAL COMPARISON OF FOUR LOW CONTACT PLATE DESIGNS FOR FIXATION OF SIMPLE TRANSVERSE FRACTURES. S. Mishra*, J. Lobo, M. Shekhman, E. Schemitsch. Division of Orthopedic Surgery, St. Michael's Hospital, University of Toronto, Canada, M5C 1R6.

Background: Adequate cortical blood flow and fracture stability are important factors in fracture healing. Newer plate designs have incorporated the limited contact principle and unicortical fixation in an attempt to reduce damage to cortical blood supply caused by bone-plate contact. Material properties of Stainless Steel and Titanium Limited Contact Dynamic Compression (LCDCP) plates have been studied by Jain *et al.* **Objective:** To determine the effect of plate design on biomechanical properties of four low contact plate designs in the fixation of midshaft transverse fractures. **Methods:** Fourteen skeletally mature pairs of canine humeri were used to compare the original Stainless Steel LCDCP (O-LCDCP) (n=7) to the Reduced Contact Stainless Steel LCDCP (RC-LCDCP) (n=7) and the Titanium LCDCP (Ti-LCDCP) (n=7) to the Titanium Point Contact Fixator plates (PCFix) (n=7). Midshaft transverse osteotomies were created in all bones, reduced, and the appropriate 8-hole plate was applied. Anteroposterior (AP) bending stiffness was determined using a four point bending jig. A 1 cm gap was created at the fracture site and AP and mediolateral (ML) bending stiffness, and yield point were determined for each construct. Contact area was determined for each plate design with pressure sensitive film. **Results:** Plate contact area was lowest for the PCFix and RC-LCDCP. We demonstrated no significant difference in the stiffness of stainless steel constructs in either plane, before or after gap creation. Before gap creation, we found no significant difference in titanium construct stiffness. However, with a gap, the Ti-LCDCP was stiffer in both planes of bending and had a higher yield point. **Conclusions:** Our results suggest that the RC-LCDCP has improved contact characteristics without any biomechanical disadvantage when compared to the O-LCDCP. This may result in a positive effect on cortical perfusion following stainless steel plate fixation. The PC-Fix may be more advantageous than the Ti-LCDCP with a fracture gap due to its reduced contact area and comparable stiffness. However, the PC-Fix is less stiff with a gap and sacrifices fracture stability for improved cortical perfusion.

SU5

DEVELOPMENT OF A SCALE TO IMPROVE RELIABILITY IN THE ASSESSMENT OF TIBIAL FRACTURE HEALING FOLLOWING INTRAMEDULLARY FIXATION.

M. Shekhman*, D.B. Whelan, M. Bhandari, E.H. Schemitsch. Division of Orthopaedic Surgery, St. Michael's Hospital, University of Toronto, Canada.

Introduction The degree of union in healing of fractures is customarily assessed by clinical and radiological means. Although several accepted methods exist to assess the state of healing clinically, no reliable guidelines are available for radiographic evaluation. Implementation of a means to quantify the progression of healing by use of a scale would improve the concordance of assessment of fracture healing between surgeons and would have important implications in standardizing outcomes in trauma. **Purpose** To evaluate the reliability of a newly developed scale to assess radiographic union in healing tibial shaft fractures treated with intramedullary nails. **Methods** Forty-five sets of AP and Lateral radiographs of tibial shaft fractures treated with intramedullary fixation at different stages of healing were selected from a trauma database. Seven reviewers (2 orthopaedic residents, 2 community surgeons, and 3 traumatologists), blinded to all aspects of patient history and clinical examination, independently scored the stage of fracture healing using the Radiographic Union Scale for Tibial Fractures (R.U.S.T.). This scale is based on a 4 to 12 point score evaluating the quality of bridging callus of 4 cortices (anterior, posterior, medial, and lateral). In addition, the radiographs were re-assessed at 8 weeks for intra-observer reproducibility. **Results** Intra-class correlation coefficients (ICC) with 95% confidence intervals were used to measure agreement. Overall agreement among all reviewers collectively was substantial. ICC=0.86 (95%CI, 0.79-0.91). Furthermore, reliability tended to be improved among traumatologists when compared to either community surgeons or residents (ICC=0.86, 0.83, 0.81, respectively). Overall intra-observer reliability for the scale was also substantial (ICC=0.88, 95%CI, 0.80-0.96). **Conclusions** The current radiographic union assessment scale exhibits substantial improvements in reliability form previously published scales. Moreover, results are equally reproducible among orthopaedic residents, community surgeons, and traumatologists.

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Acknowledgements

The Faculty of Medicine gratefully acknowledges support from the following companies:

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